

CHEMOENZYMATIC APPROACH TO THE SYNTHESIS OF THE  
MORPHINAN SKELETON VIA A CLAISEN REARRANGEMENT APPROACH

By

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Dedicated to

Nana Akua and Akwasi

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## ABSTRACT

Abstract of Dissertation Presented to the Graduate School  
of the University of Florida in Partial fulfillment of the  
Requirements for the Degree of Doctor of Philosophy

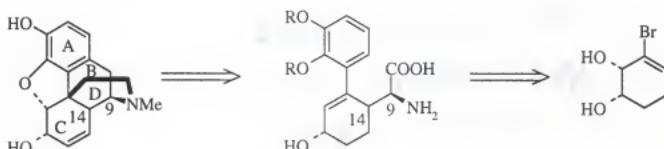
## CHEMOENZYMATIC APPROACH TO THE SYNTHESIS OF THE MORPHINAN SKELETON VIA A CLAISEN REARRANGEMENT APPROACH

By

Kofi Oppong

August 2001

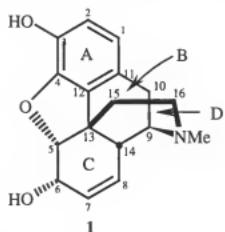
Chairman: Dr. Tomas Hudlicky  
Major Department: Chemistry



An approach to the morphinan skeleton with complete control of the C9 and C14 stereocenters is described. The first generation of the synthesis of the A and C rings of morphine are discussed. Also described are attempts at establishing the C13 quaternary center with emphasis on construction of the D-ring. The use of precursors from the enzymatic biooxidation of aromatic compounds in the construction of the morphinan skeleton through various chemical modifications is reported.

## CHAPTER 1 INTRODUCTION

Morphine (**1**), one of the world's oldest drugs, is consumed to the tune of one hundred metric tons in the United States alone annually.<sup>1-4</sup> Its main legal uses is for pain relief in cases of severe trauma (caused by the agonist binding to the  $\mu$ - receptors in the



central nervous system). These receptors are responsible for analgesia, euphoria, addiction and respiratory depression. In recent years morphine has been used in high doses as an anaesthetic in open-heart surgery due to its ability to slow down respiratory activity without affecting cardiac function.

Morphine is the major component (20%) of the opium of the poppy, *Papaver somniferum*,<sup>4</sup> and its documented use dates back to 1500 BC<sup>5</sup> and its impact on society has been quite remarkable. On average 20 people per day die of drug abuse across Europe. In 1999 alone the opium harvest in Afghanistan, a country illegally harvesting morphine, was 4581 metric tons. Legally opium is harvested in India (the only legal producer) on a multi-ton scale. The alkaloid constituent of the opium poppy is about

25%; of this, two of the important alkaloids, morphine (**1**) and codeine (**2**), constitute approximately 17%.<sup>6</sup>

Although morphine is quite abundant from the isolation of the natural resource, it still remains a viable synthetic target to various research groups around the world. The focus is not only to find an efficient synthesis of morphine but more importantly to arrive at a more practical synthesis of the morphinan skeleton, which would allow for a more competent route to some the important derivatives of morphine.

Of the twenty-one formal synthesis of morphine only three syntheses have used sigmatropic rearrangements as key steps. Interestingly, the rearrangements were all used to install the quaternary center at C13. None of the above approaches used the rearrangement to transfer stereochemistry inherent in the molecule to another site with the result of correctly setting two important stereocenters in one transformation.

This thesis describes a Claisen rearrangement approach to the synthesis of the morphinan skeleton. Control of the stereo centers C9 and C14 are discussed and recent advances in the synthesis of the morphinan skeleton are also reported.

## CHAPTER 2

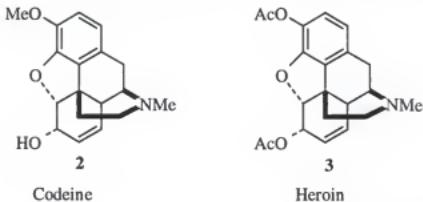
### HISTORICAL BACKGROUND

#### Introduction

According to the available records, the relationship between opium and human beings started in ancient Middle Eastern civilizations about 3500 years ago.<sup>6</sup> Since then the potent bioactivity of morphine and its derivatives was an important issue that has crossed the frontiers of medicine and become a socio-political factor. In the sixteenth century, Parcellus popularized the use of opium as an analgesic when he introduced various preparations and named it “laudanum” which is derived from the latin word meaning to praise.

Although opium had been used for centuries, morphine was not isolated as a crystalline material until 1803 as reported by Derosne.<sup>8,9</sup> Three years later in 1806, Seguin presented a description of the isolation of morphine to the Institute of France,<sup>10</sup> and later in the same year, Serturner was finally credited with the first isolation of crystalline morphine.<sup>11</sup> A century later in 1925, Sir Robert Robinson postulated the correct structure of morphine including relative stereochemistry.<sup>12</sup> This was later confirmed by X-ray crystallographic analysis in combination with other analytical techniques.<sup>13,14</sup> After its isolation morphine 1 was introduced into medical practice and used extensively to treat ailments such as diarrhea, asthma, diabetes, ulcers and pain relief. Bayer at the end of the nineteenth century was marketing diacetyl morphine

(Diamorphine).<sup>14</sup> It was nicknamed heroin because it was considered a “heroic” drug. Heroin **3** has the same physiological effects as morphine (because of rapid hydrolysis to morphine, most of its actions are due to morphine itself) except that it acts faster and is more potent. However there are appropriate differences. Heroin is lipid soluble and rapidly enters the brain. Morphine is not as lipophilic and hence its passage to



**Scheme 2**

the brain occurs at a much slower rate. Codeine **2** is approximately one-sixth as effective as morphine as an analgesic. It is best administered orally and acts as a good cough suppressant.

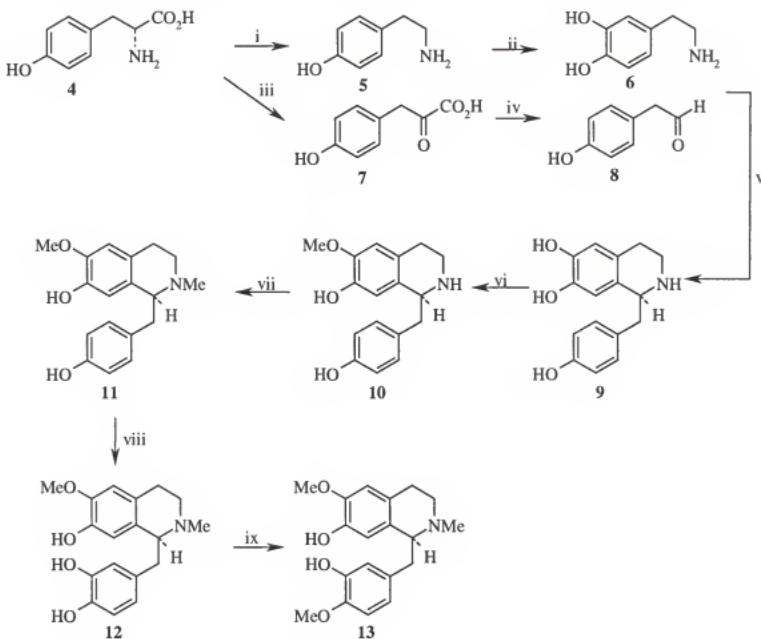
In 1952, Gates achieved the first total synthesis of morphine<sup>15,16</sup> and confirmed the structure of morphine as proposed by Robinson. Since Gates historic synthesis, about 20 formal syntheses of morphine have been reported. In spite of these reports and 150 years of effort since its discovery, a truly practical synthesis, which would compete economically with the isolation of morphine directly from the opium poppy, *Papaver somniferum*, has not yet been achieved.

Astonishingly, of all the reported formal synthesis of (-)-morphine to date only three have used some sort of sigmatropic rearrangement. Only the syntheses of Rapoport,<sup>17,18</sup> Parsons,<sup>19,20</sup> and Mulzer<sup>21-25</sup> have relied on these types of reactions. Interestingly, the three syntheses made use of the rearrangement for the same purpose: to install the

quaternary center at C13 (morphine numbering), while transferring the stereochemistry already present in the starting material to that position.

### Morphine Biosynthesis

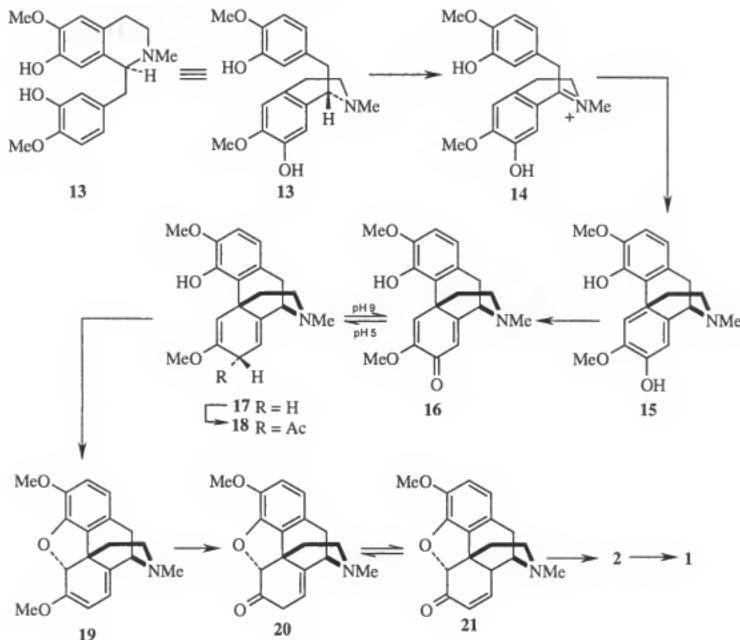
It is interesting to note that Robert Robinson, who proposed that morphine consisted of a twisted benzylisoquinoline skeleton, made one of the most important



**Scheme 3**

Enzymes: i) L-tyrosine decarboxylase; ii) phenolase; iii) L-tyrosine transaminase; iv) *p*-hydroxyphenylpyruvate decarboxylase; v) (*S*)-norcoclaurine synthase; vi) norcoclaurine-6-*O*-methyltransferase; vii) tetrahydrobenzylisoquinoline-*N*-methyltransferase; viii) phenolase; ix) 3'-hydroxy-*N*-methyl (*S*)-coclaurine-4'-*O*-methyltransferase.

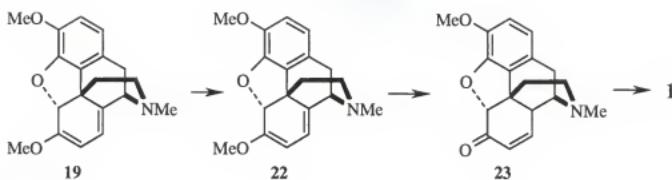
observations that eventually led to the elucidation of the structure of morphine.<sup>12,26</sup> Studies conducted on the biosynthesis of morphine indicate that the morphinan alkaloids are formed by a series of benzylisoquinoline intermediates (Scheme 3) which eventually forms (R)-reticuline **14** (Scheme 4).<sup>27,28</sup>



Scheme 4

The benzylisoquinoline skeleton is derived from two molecules of L-tyrosine (**4**), which is converted into a molecule each of dopamine **6** and 4-hydroxy phenylacetaldehyde **8** through the intermediacy of tyramine **5** and 4-hydroxyphenyacetic acid **7** respectively (Scheme 3). Condensation of these two derivatives of L-tyrosine is catalyzed in a stereospecific manner by (S)-noroclaurine synthase, which results in the

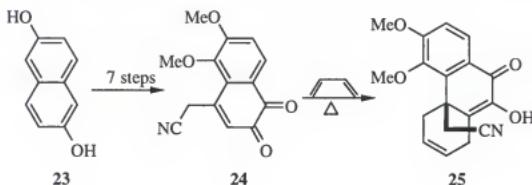
formation of (*S*)-norcoclaurine **9**, which serves as the skeletal foundation of most of the benzylisoquinoline alkaloids. The next three steps can be summarized as two enzyme-catalyzed methylations and an aromatic hydroxylation to afford (*S*)-reticuline **13**, that possesses the opposite configuration to the compound found in the biosynthesis of morphine (what would be the C9 center of morphine has the opposite stereochemistry). Inversion to the correct intermediate is effected in two steps through the intermediate imine dehydroreticuline **14** (Scheme 4) by a highly stereospecific and NADPH/NADPH<sup>+</sup> dependent reductase to afford (*R*)-reticuline **15**.<sup>29,30</sup> It is likely that the mechanism involves the formation of two phenolate radicals and their subsequent coupling. The next step in the biosynthesis is the conversion of (*R*)-reticuline into salutaridine **16** by a membrane-bound cytochrome P-450 enzyme whose catalytic action is strictly dependent on NADPH and molecular oxygen. After the formation of salutaridine **16**, the ketone moiety is reduced by an NADPH-dependent oxidoreductase to afford salutaridinol **17**,<sup>31</sup> which then undergoes enzyme-catalyzed acetyl CoA dependent acetylation to yield the acetate **18**.<sup>32</sup> The next intermediate formed is thebaine **19**, which results from ring closure at slightly basic pH. Failure to find a specific enzyme for this step has led to the conclusion that this step is spontaneous. Neopinone **20** is formed by the demethylation of thebaine to form the ketone, which is in chemical equilibrium with codeinone **21**. The final steps in the morphine biosynthesis are the conversion of codeinone to codeine (**2**) and a final demethylation of codeine to afford morphine (**1**). An alternate pathway to morphine has also been proposed and it involves arriving at the target first by demethylation of thebaine to obtain the intermediate alcohol **22**, then conversion to the enone **23** whose reduction by codeinone reductase affords morphine **1** (Scheme 5).<sup>33,34</sup>



Scheme 5

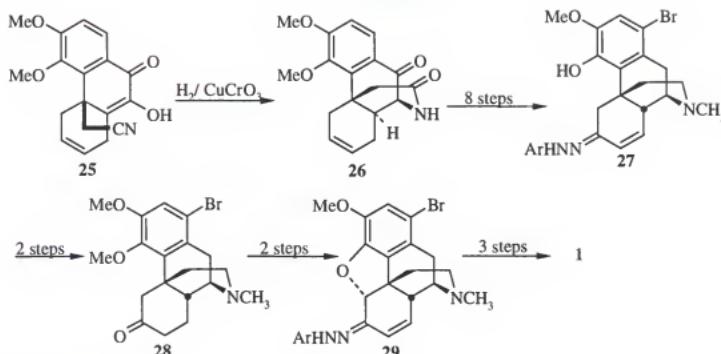
### Total and Formal Synthesis of Morphine

Gates landmark synthesis of morphine in 1952 started from naphthalene



Scheme 6

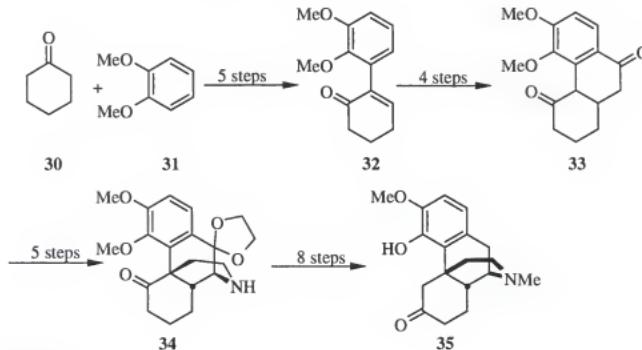
diol 23, which was subsequently converted over seven steps to the substituted naphtoquinone 24 (Scheme 6).<sup>15,16</sup> The [4+2] cycloaddition of 24 with 1,3-butadiene under thermal conditions afforded the phenanthrene 25. Phenanthrene 25 was subjected to hydrogenation in the presence of copper chromite which led to an unexpected cyclization affording tetracyclic amide 26. Although the stereochemistry at C9 (morphine numbering) was set correctly during the cyclization, it was necessary to epimerize the C14 (morphine numbering) center (Scheme 7). Gates, while attempting to close the furan ring *via* alpha bromination of the corresponding ketone, achieved this epimerization with dinitroarylhydrazone 27, the most commonly intercepted intermediate in subsequent formal morphine syntheses. The furan ring was then closed to afford pentacycle 29 and



**Scheme 7**

completed the construction of the morphine skeleton. Finally, hydrolysis, lithium aluminum hydride reduction, and demethylation completed the first total synthesis of morphine 1.

Shortly after Gates' historic synthesis, Ginsburg completed a formal synthesis by synthesizing dihydrothebainone **35** in 1954.<sup>35</sup> In Ginsburg's synthesis, condensation of

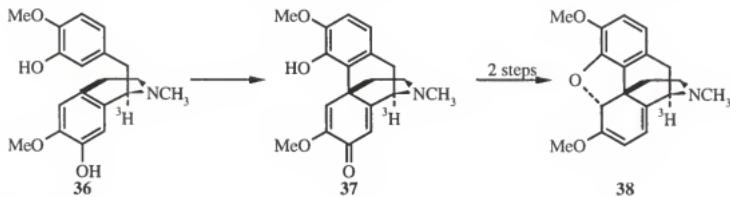


### Scheme 8

veratrole **31** via ortho-lithiation to cyclohexanone **30** served as the first step (Scheme 8).

The coupled product was dehydrated and then converted to enone **32**. Michael addition with dibenzyl malonate, followed by decarboxylation and a Friedel-Crafts annulation resulted in the formation of the phenanthrenone **33**. Finally the D ring was installed using a series of steps culminating in the spontaneous formation of the ethylamine bridge accompanied with cleavage of the C4 methyl ether and formation of the tetracyclic amide **34**. An additional 8 steps followed by *d*-tartaric acid resolution yielded (-)-dihydrothebainone **35**, and consequently, the first of many formal synthesis of morphine.

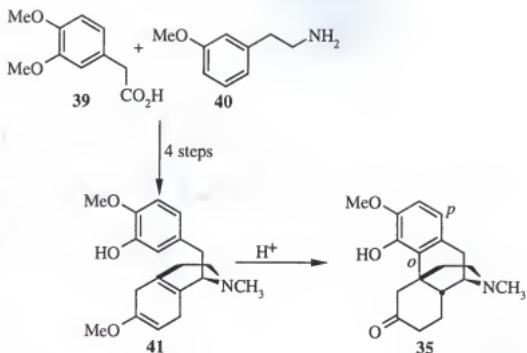
Nine years later, Barton presented a biomimetic synthesis of a radio labeled thebaine **38** (Scheme 9).<sup>36</sup> Starting from tritium labeled reticuline **36** he performed an MnO<sub>2</sub> promoted oxidative coupling to construct the phenanthrene core. However this step



Scheme 9

proceeded in a poor yield and after two additional steps a radioisotope dilution study of the final thebaine **38** was performed to establish a 0.012% conversion of tritium labeled salutaridine **37**.

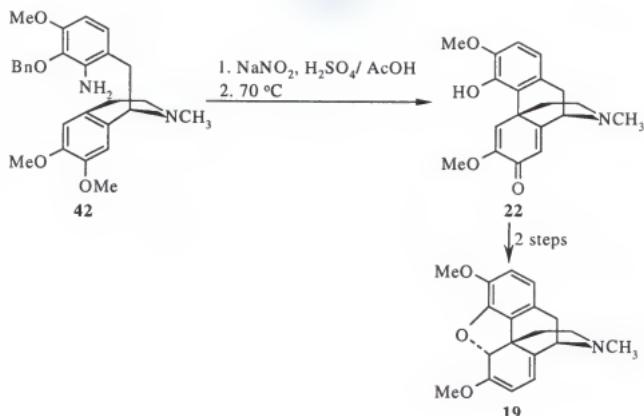
Simultaneous reports presented in 1967 by Grewe<sup>37-38</sup> and Morrison, Waite and Shavel<sup>40</sup> collectively, established a successful path for the coupling of rings A and C (Scheme 10).

**Scheme 10**

Substituted benzyltetrahydroisoquinoline **41** was readily obtained after a Birch reduction of the coupled product of compounds **39** and **40**. Grewe then used phosphoric acid, while Morrison, Waite and Shavel were successful with 10% aqueous HCl, to render the *ortho* coupled product in 3% yield. The *para* product was obtained in 37% yield. This process resulted in the formation of dihydrothebainone **35**.

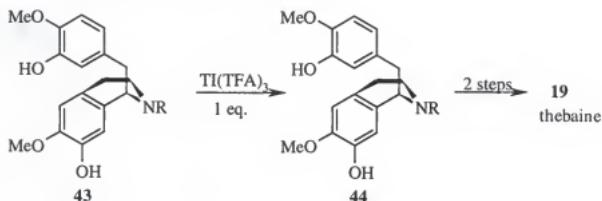
Other research groups later improved the ortho selectivity of the Grewe cyclization, and this disconnection is found in several of the following formal synthesis.

Kametani<sup>41</sup> utilized a Pschorr type cyclization in his approach to thebaine **19** to maximize the *ortho*- *para* selectivity (Scheme 11). Diazotization of 2-aminobenzyl tetrahydroisoquinoline **42** followed by thermal decomposition yielded racemic salutaridine **16** in a yield of 1.1%, however no *ortho*-*ortho* products were observed.



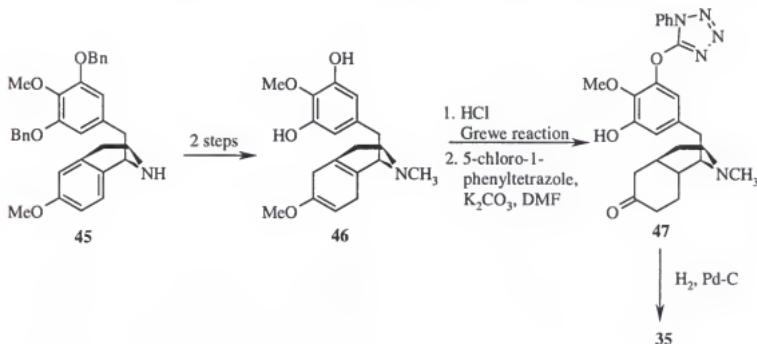
**Scheme 11**

Schwartz,<sup>42,43</sup> in a biosynthetically designed synthesis, used thallium (III) trifluoroacetate to effect the *ortho-para* coupling of N-acynorreticuline **43**, affording the corresponding salutaridine derivative **44** (Scheme 12). Reduction of this intermediate with LiAlH<sub>4</sub> followed by O-ring closure with HCl resulted in the formation of thebaine and resulting in a formal total synthesis.



### Scheme 12

Beyerman<sup>44</sup> used a Grewe type cyclization with a symmetric arene to overcome selectivity problems (Scheme 13). The N-methylation of benzyl protected phenol **45**,

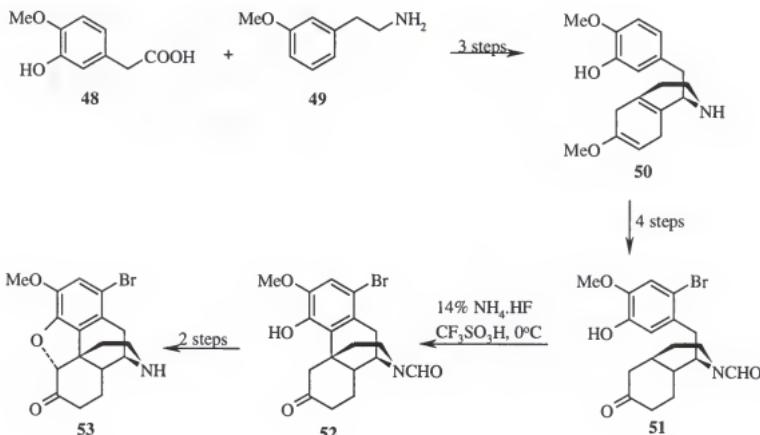


Scheme 13

followed by hydrogenation and finally a Birch reduction rendered tricycle **46**, which readily cyclized in the presence of HCl to **47**. Fortunately, the additional hydroxyl group at C2 in **47** was selectively removed by conversion to the corresponding tetrazole ether followed by hydrogenolysis, which afforded dihydrothebainone **35** and formalized Beyerman's synthesis.

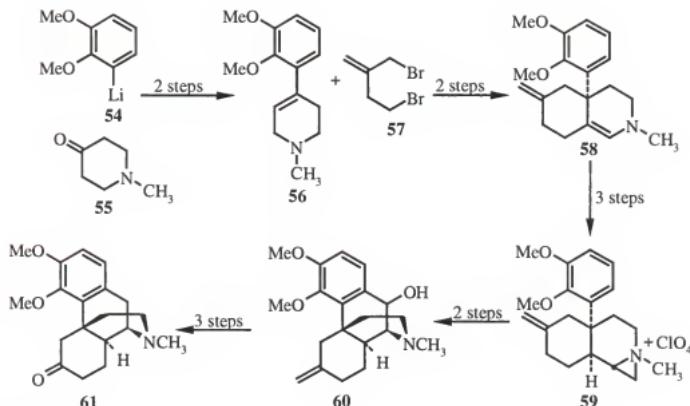
Rice<sup>45</sup> is given credit for the most practical synthesis of morphine to date, with an overall yield of 29%. Using starting materials similar to those used by Grewe and Morrison, Rice was able to synthesize amine **50** by coupling of acid **48** and amine **49**. In 3 steps Rice was able to synthesize bromide **51** using a strategy similar to that of Beyerman. This was a key intermediate because it possessed a well placed bromine substituent, which blocked *para* cyclization. Bromonordihydrothebaine **52** was formed in 60% yield, and was eventually converted to dihydrocodienone **53** (Scheme 14). Overall

the whole synthesis required isolation of only six intermediates, obtained in sufficiently pure form to continue with the synthesis. It still remains the most practical synthesis to date.



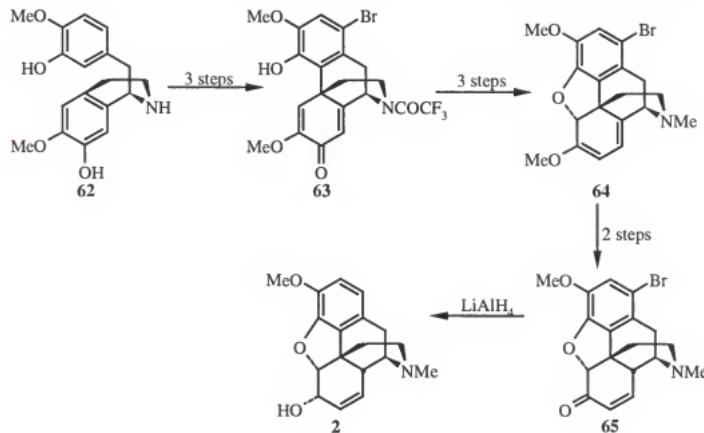
Scheme 14

In 1983, Evans<sup>46</sup> used the ortho lithiated veratrole **54** in an initial coupling reaction with piperidone **55** in his approach (Scheme 15). After the coupling, dehydration afforded alkene **56**, which was further coupled with dibromide **57**. Isoquinoline **58** was then converted to the aziridinium salt **59**, which was then opened, oxidized to an aldehyde and finally treated with Lewis acid to form the morphinan **60**. Removal of the C10 hydroxyl group followed by oxidation afforded ketone **61**, which is one of Gates' intermediates hence resulting in a formal synthesis.



Scheme 15

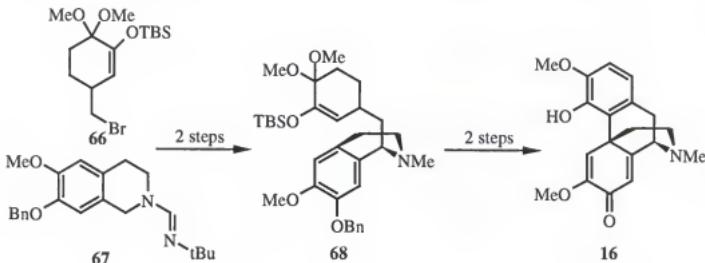
A third report in 1983 by White<sup>47</sup> described an oxidative coupling approach to (-)-codeine **2** (Scheme 16). After protection and bromination, (-)-Norreticuline **62**,



Scheme 16

underwent successful and selective *para-para* coupling to afford salutaridine analogue **63**, which was further manipulated to bromothebaine **64**. Simple hydrolysis followed by double bond migration afforded the Gates intermediate **65** which on treatment with LiAlH<sub>4</sub> gave (-)-codeine **2**.

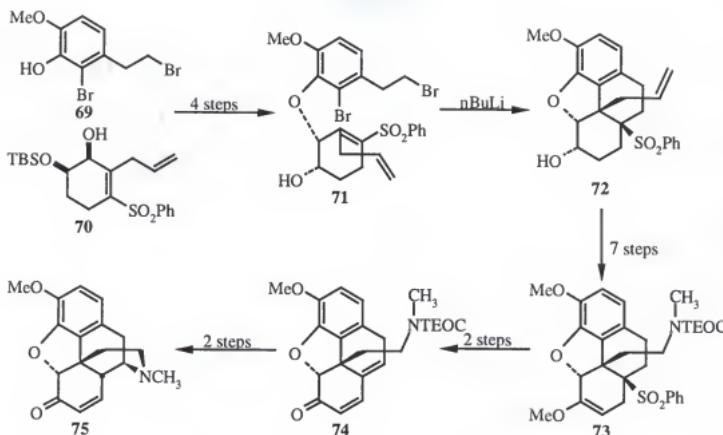
In 1986, Schafer<sup>48</sup> reported another oxidative coupling approach to salutaridine (Scheme 17). Formamidine **67** was coupled with bromide **66** and the product



Scheme 17

reductively cleaved to afford the cyclization precursor **68**. Cyclization was achieved using TiCl<sub>4</sub> and subsequent rearomatization of the A-ring using DDQ afforded salutaridine **16** in 3% overall yield in 15 steps.

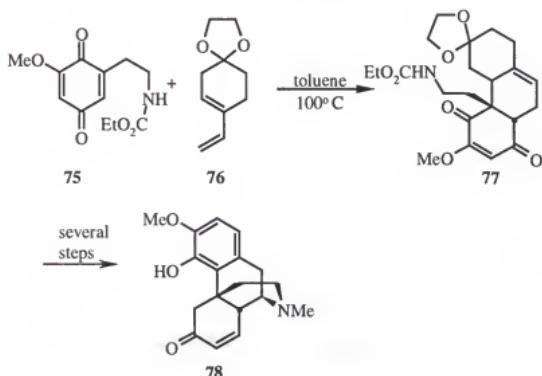
In 1987, Fuchs<sup>49</sup> reported a total synthesis of morphine using a tandem coupling reaction to construct the morphinan skeleton. His approach to the morphinan skeleton used an intramolecular conjugate addition/alkylation sequence in which connections C12-C13 and C9-C14 were formed as a result of one-tandem process. Coupling of aryl **69** to alcohol **70** under Mistunobu conditions followed by deprotection and an oxidation/reduction sequence afforded ether **71** with the desired *cis* stereochemistry (Scheme 18). The tandem cyclization was achieved by treatment of ether



Scheme 18

**71** with *n*-BuLi, which led to the closure of the C12- C13, bond and subsequently underwent alkylative closure of the final ring to yield the tetracycle **72**. After oxidative cleavage of the olefin to the corresponding aldehyde the nitrogen was introduced by reductive amination and protected as the trimethylsilylethoxycarbonyl ester, and finally oxidation followed by enol ether formation afforded **73**. Base catalyzed elimination of the sulfonyl group followed by oxidation with DDQ gave dienone **74**. Upon removal of the protecting group, a 1,6-Michael type addition afforded codeinone **21** as well as the nonconjugated neopinone, which could be readily isomerized to codeinone under conditions reported by Rapoport and Barber.<sup>50</sup> Fuchs completed his total synthesis by converting codeinone to racemic morphine with reduction and final demethylation.

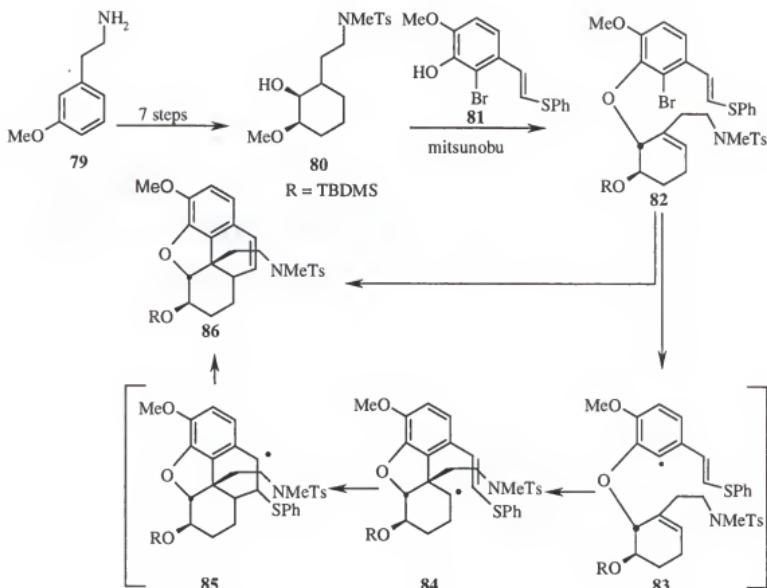
In 1992, Tius<sup>51</sup> used an intermolecular Diels-Alder reaction as an early step in his formal synthesis. Quinone **75**, which was prepared in 7 steps from 3-methoxy-2-hydroxy



Scheme 19

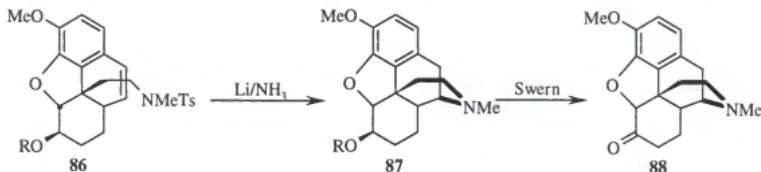
benzaldehyde, was heated with diene **76**, prepared in 2 steps from 1,4-cyclohexanedione monoethylene ketal, to construct phenanthrene **77** (Scheme 19). After several subsequent steps Tius completed his synthesis by constructing thebainone **78**, thus intercepting Gates' approach.

Parker and Fokas<sup>52</sup> accomplished a well designed formal synthesis of morphine in 1993. Their approach hinged on an efficient radical cascade which in one step led to the construction of a morphinan complete with the A, B, C and O-rings of morphine (Scheme 20). To be able to take advantage of this tandem cyclization strategy, they had to first construct aryl ether **82**, through an eight-step sequence starting from m-methoxy phenethylamine **79** and culminating in a Mitsunobu coupling of the resultant alcohol **80** with phenol **81**. With the aryl ether in hand the ortho allyloxy aryl radical **83** was generated using tributyltin hydride/ AIBN. Tandem closure led to isolation of



Scheme 20

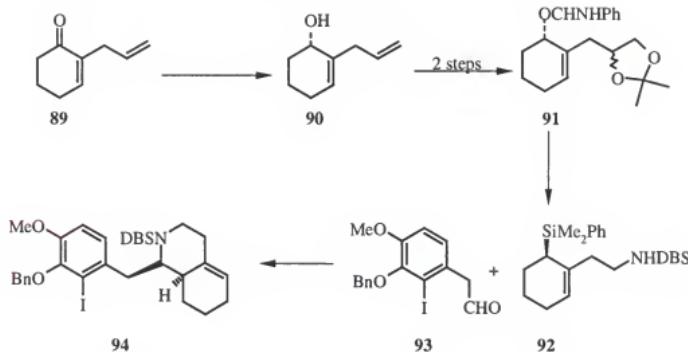
tetracycle **86** in 35% yield by initial attack of the radical on the proximal but more substituted end of the cyclohexyl ring double bond to establish the furan ring with the correct stereochemistry at C13. The radical generated in the formation of the furan



Scheme 21

ring then attacked the  $\beta$ -carbon of the styrene double bond to give rise to the resonance stabilized radical of **85** with the correct stereochemistry at C14. Final elimination of the phenylthio group from **85** led to formation of styrene **86**. Dihydroisocodeine was formed when the tosylamide **86** was treated with Li/NH<sub>3</sub> at -78° C. Swern oxidation of dihydroisocodeinone **87** afforded dihydrocodeinone **88**, which then completed her approach.

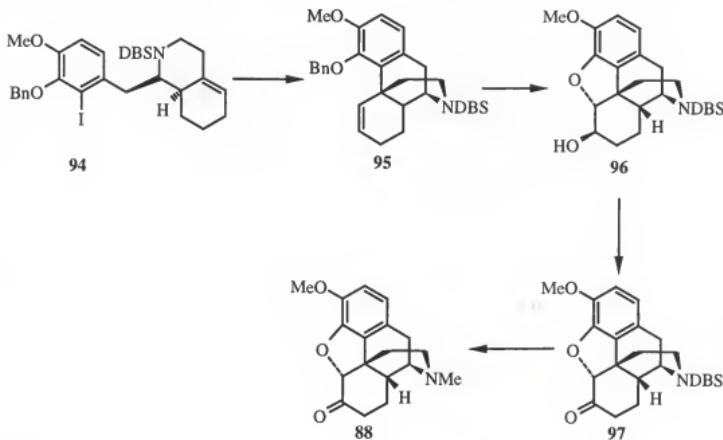
The crucial step in Overman's<sup>53</sup> approach was essentially a Grewe type disconnection, but involved an intramolecular Heck reaction to complete the construction of the B-ring. The synthesis started with enantioselective reduction reduction of 2-allyl cyclohexenone **89** which would introduce chirality into the synthesis. Condensation of the resultant *S*-alcohol **90** with phenylisocyanate, oxidation of the side chain olefin with osmium tetroxide and acetonide protection afforded **91** (Scheme 22).



**Scheme 22**

A copper catalyzed suprafacial S<sub>N</sub>2' displacement of the allyl carbamate with lithium dimethylphenyl silane, deprotection and diol cleavage yielded an intermediate aldehyde, which then underwent reductive amination with dibenzosuberyl amine to afford **92**.

Condensation of allylsilane **92** with iodide **93** (prepared in 7 steps from isovanillin in an overall 62% yield) at 60 °C in the presence of ZnI<sub>2</sub> followed by iminium ion-allylsilane cyclization yielded the isoquinoline intermediate **94**. Palladium mediated coupling led to the formation of the C12-C13 bond and morphinan **95** (Scheme 23) with the correct stereochemistry at C9, C13, and C14. Liberation of the phenolic oxygen and β-face epoxidation of the C6-C7 double bond and subsequent intramolecular ring-opening by the phenolic hydroxyl completed the dihydrofuran ring. Oxidation followed by reductive DBS cleavage in the presence of formaldehyde yielded (-)-dihydrocodeinone **88**.



Scheme 23

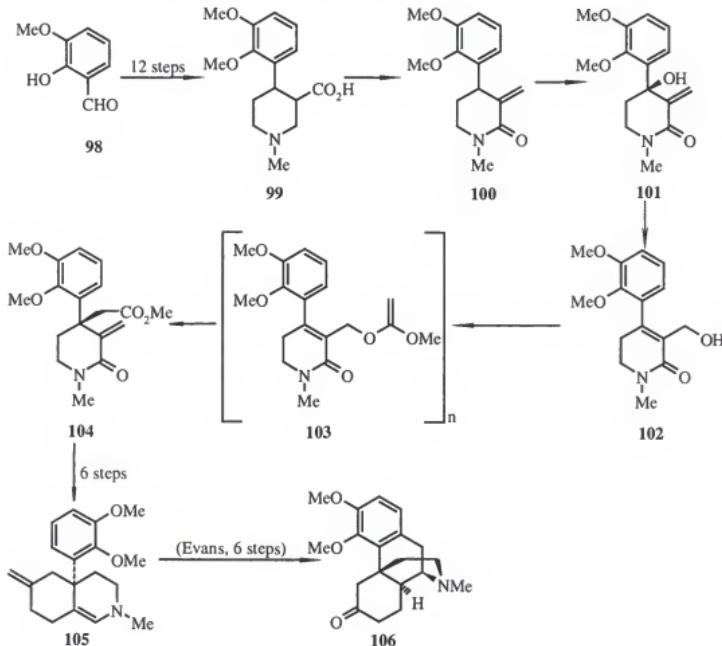
#### Morphine Syntheses via Sigmatropic Rearrangements

Although a wide variety of synthetic approaches have been applied to the morphine problem, sigmatropic rearrangements have rarely been elicited as synthetic tools. Of the more than twenty formal syntheses only three, namely those of Rapoport,<sup>50</sup>

Parsons<sup>20</sup> and recently Mulzer<sup>21-25</sup> were able to utilize sigmatropic rearrangements as key steps in their approaches to morphine.

Interestingly, all three approaches used the sigmatropic rearrangement for the same purpose, to install the quaternary center at C13 (morphine numbering) while transferring the stereochemistry already present in the starting material to that position.

Rapoports' synthesis began with the conversion of *ortho*-vanillin **98** to amino acid **99** in twelve steps (Scheme 24). The amino acid then underwent rearrangement in the

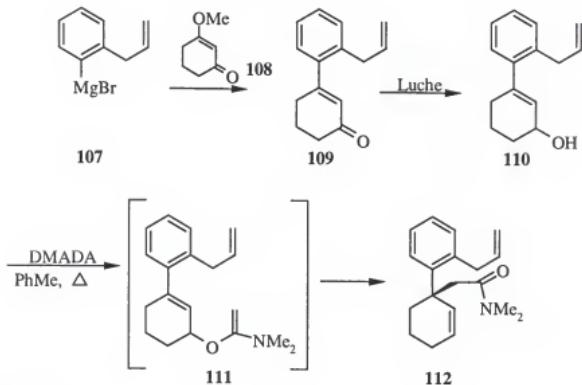


Scheme 24

presence of acetic anhydride to afford lactam **100**. Benzylic oxidation followed by reaction with formic acid yielded, after allylic migration and hydrolysis, alcohol **102**. Condensation of the alcohol with trimethyl orthoacetate produced acetal **103**, which subsequently underwent rearrangement to afford the methyl ester **104**. This compound contained the required quaternary center at C13 as well as the complete C ring with an adequate pattern of substitution. Ring B was emergent in this structure but required more steps to develop.

After several attempts, Rapoport decided to intercept the advanced Evans intermediate **105** from which Evans was able to synthesize one of Gates advanced intermediates (**106**) in six additional steps.

Parsons,<sup>20</sup> in 1984 reported the synthesis of the precursor **113**, through an interesting sequence. Their synthesis started with the 1,2 addition of the Grignard

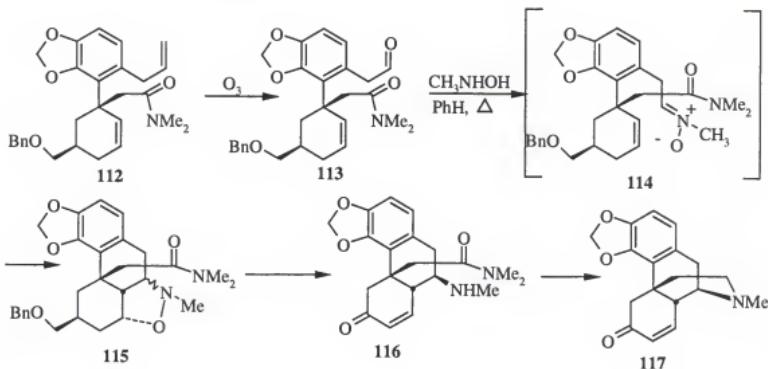


Scheme 25

compound **107**, to ketone **108**. After hydrolysis, the product **109** was reduced using Luche condition to obtain the alcohol **110**, which was condensed with dimethylacetamide

dimethyl acetal to form the acetamido acetal **111**. Concomitant rearrangement of **111** via an Eschenmoser-Claisen rearrangement gave the amide **112** (Scheme 25). Using this series of transformations, Parsons and Chandler were able to set the stereochemistry at C13 correctly.

Closure of ring B was achieved starting with the ozonolysis of **112** which resulted in the aldehyde **113**, which was consequently treated with N-methyl hydroxylamine

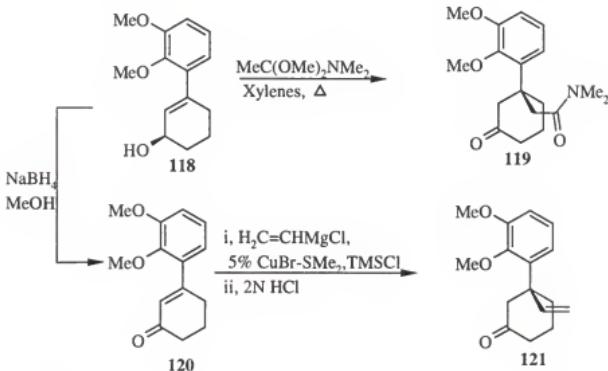


Scheme 26

to yield the intermediate **114**. The intermediate then accordingly rearranged to produce the isoxazolidine **115** through an intramolecular cycloaddition with an overall 72% yield. The cycloaddition product possessed the correct stereochemistry at C14 but was epimeric at C9. The resultant epimers were separated using chromatography and the N-O bond of the morphine-like isomer was cleaved by hydrogenolysis to produce the amino alcohol **116**. The morphinan **117** (Scheme 26) was obtained by heating the resulting hydrochloride salt of **116** under vacuum followed by LAH reduction of the resulting hydroxy amide produced the morphinan **117** with an overall yield of 2.1%.

In Mulzer's<sup>21-25</sup> synthesis of morphine, a creative approach towards the morphine skeleton was employed. In the first generation of the synthesis he used a model study to explore the possibility of establishing the important benzylic quaternary stereogenic center (C13) via either conjugate addition of a cuprate to an unsaturated ketone or [3,3]-sigmatropic rearrangement.

Starting from alcohol **118** Mulzer and co-workers attempted an Eschenmoser-

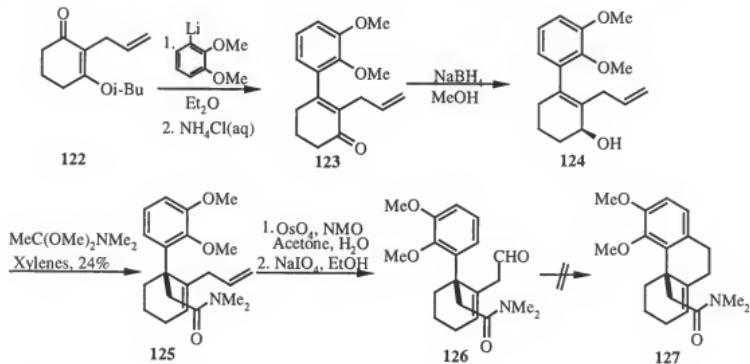


Scheme 27

Claisen rearrangement to obtain amide **119** in only 21% yield. With this unsatisfactory result they tried both the Ireland and the Johnson variants of the Claisen rearrangement on the alcohol **120** that was obtained after reduction of the enone, both failed completely.

An explanation for this might be strong conjugation of the double bond (C5-C13 morphine numbering) to the aromatic ring. Since Claisen rearrangements and 1,4-additions of vinyl cuprates are complementary to each other, the latter was attempted on the enone **120** with positive results, leading to the formation ketone **121** in 87% yield over 2 steps.

Another interesting discovery was made during this model study. After preparing a more elaborate substrate **124** from the addition of ortholithiated veratrole to the vinylogous ester **122** followed by hydrolysis and dehydration. Enone **123** after reduction was subjected to Eschenmoser-Claisen rearrangement conditions. The results were similar, even though rearranged product was obtained the yields were low. More interestingly after cleavage of the terminal double bond of amide **125** (Scheme 28) to obtain the aldehyde **126**, all attempts at closing the B- ring failed completely. Mulzer explained these results using the theory that repulsive interactions between the *ortho*-methoxy group and the substituents  $\alpha$ -to the C13 carbon (morphine numbering) on the cyclohexyl ring. This steric interaction causes the aromatic ring to twist out of conjugation with the double bond in the cyclohexyl ring. This assumption had merit because  $^1\text{H}$ - NMR of the allylic alcohol clearly showed the two rotomers reminiscent

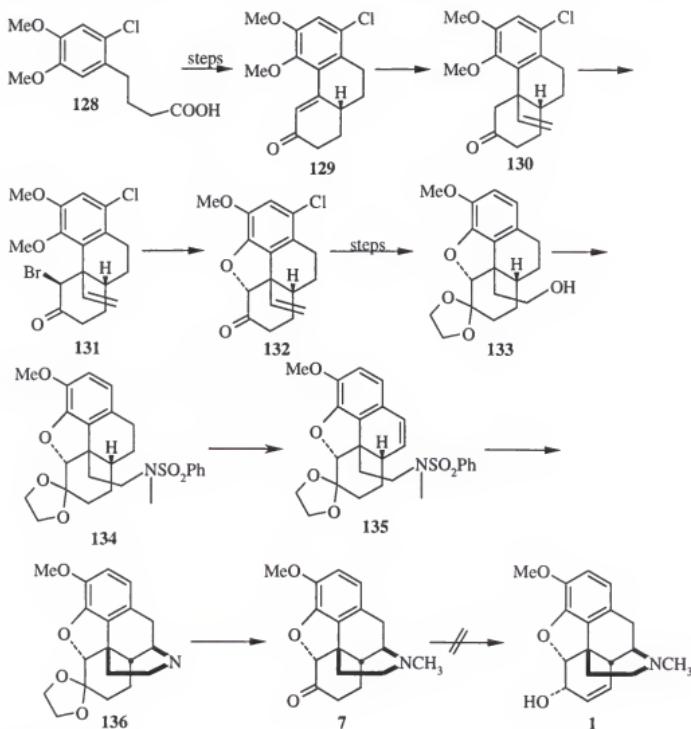


Scheme 28

of the known atropisomerism found in biphenyls. The result is a highly adverse steric influence at the benzylic  $\text{sp}^2$  -hybridized carbon by the aromatic ring. The apparent

solution to this setback was to restrict the conformational flexibility of the aromatic ring by means of a tether, which would also provide the two-carbon fragment for the B-ring. This idea led to the synthetic pathway that would eventually result in the synthesis of the morphine skeleton by way of phenanthrone **129**. Starting from enantiomerically pure phenanthrone **129**, which was synthesized in 3 steps from acid **128**, conjugate addition with a variety of functionalized organocuprates provided good yields of the olefin **130**. Mulzer and co-workers discovered that the substitution pattern on the aromatic ring was critical in obtaining clean 1,4-adducts. With olefin **130** in hand they were able to effect E-ring closure using a clever “umpolong” strategy. After trapping the ketone as the silyl enol ether, bromination with NBS in THF at low temperature yielded bromoketone **131** as a 3:1 isomeric mixture. The undesirable isomer could however be recycled by way of reductive removal of bromide with zinc and concomitant silylation of the resultant enolate. When  $\alpha$ -bromoketone **131** was heated in DMF at 140°C the dihydrofuran was obtained in 20 minutes in quantitative yield. The next stage in the synthesis involved the introduction of the nitrogen functionality at C9 (morphine numbering). Ketone **132** was subjected to a three step sequence that resulted in a) protection as the ethylene ketal b) hydroboration of the vinyl group with  $\text{BH}_3\cdot\text{SMe}_2$  followed by oxidation and c) removal of the chloro substituent by catalytic hydrogenation to render alcohol **133**. The alcohol was then converted to the benzene sulfonamide derivative **134** using a variation of the Mistunobu protocol which uses *N*-methylbenzene sulfonamide, 1,1'-azodicarbonylpiperidine (ADDP) and  $\text{Bu}_3\text{P}$ . The next step was to introduce a double bond by benzylic radical bromination followed by debromination. Hence exposure of **134**

to NBS and catalytic amount of dibenzoyl peroxide in refluxing carbon tetrachloride



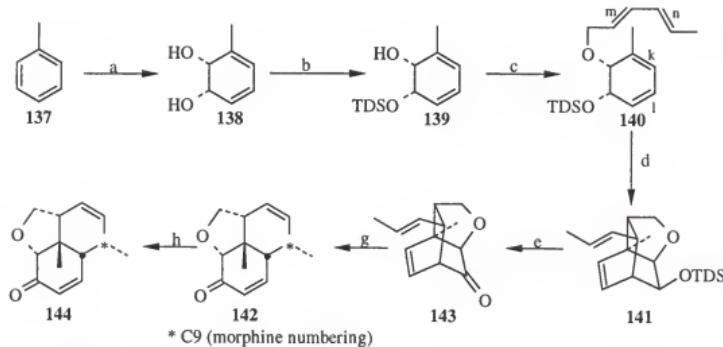
Scheme 29

afforded the “morphimethine”. Treatment of the styrene 135 under reductive conditions ( $\text{Li}/\text{NH}_3/\text{THF}$ ) yielded the desired heterocyclization product, (-)-dihydrocodeinone 88 after hydrolysis of the ketal 136 using 3N HCl. Unfortunately attempts to convert dihydrocodeinone to morphine failed probably because of competing oxidation of the tertiary amine followed by polymerization. In 13 steps and an overall 11.5 % this make Mulzers’ synthesis one of the most practical of all attempts at morphine synthesis.

### Recent Related Developments

In addition to the Claisen approach to the morphine skeleton, the Hudlicky group is actively pursuing two other approaches toward the morphinan skeleton namely an intramolecular Diels-Alder approach and a Heck coupling cascade approach.

Hudlicky, Boros and Boros<sup>54</sup> were able to synthesize the B-, C-, and O- rings using a combination of three important transformations, microbial oxidation, intramolecular Diels-Alder cycloaddition and a Cope rearrangement. Starting from toluene, which was subjected to microbial oxidation to yield diol 138, protection of the distal hydroxyl group afforded the thexyldimethylsilyl ether 139. Alkylation of the proximal hydroxyl group with sorbyl bromide rendered the tetraene 140. The substrate was now ready for an intramolecular Diels-Alder reaction. The Diels-Alder

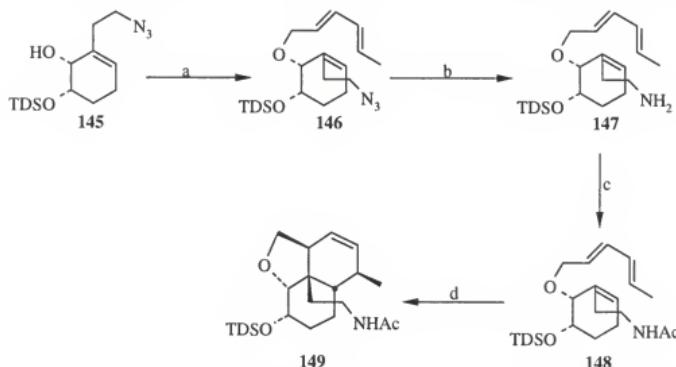


**Scheme 30** Conditions: a) Toluene dioxygenase; b) THSCl, imidazole, DMF; c) NaH, sorbyl bromide, THF, 0° C to rt., 30h.; d) CCl<sub>4</sub>, 77° C, 7h.; e) nBu<sub>4</sub>NF-3H<sub>2</sub>O, THF; f) PCC, CH<sub>2</sub>Cl<sub>2</sub>, rt.; g) xylenes, sealed tube, 250° C, 22h.; h) NaBH<sub>4</sub>, CeCl<sub>3</sub>-7H<sub>2</sub>O, MeOH, rt., 15 min.

reaction could possibly take two reaction pathways namely, diene k, l with dienophile m (Scheme 30) or diene m, n with dienophile k. The latter reaction pathway involving diene

m,n and dienophile k was observed to yield furan **141**. Attempts to induce Cope rearrangement to form the desired tricyclic compound **142** were unsuccessful. To supply some driving force for the Cope rearrangement, the THS-ether was converted in two steps into the ketone by first fluoride deprotection of the silyl group followed by PCC oxidation to afford ketone **143**. The ketone successfully underwent the rearrangement to afford enone **142**. Reduction using Luche conditions produced compound **144** that possesses the carbon skeleton for the lower half of morphine with all the stereocenters correctly set with the exception of what would be C9 (morphine numbering).

Hudlicky and Gum<sup>55</sup> published a second generation intramolecular Diels-

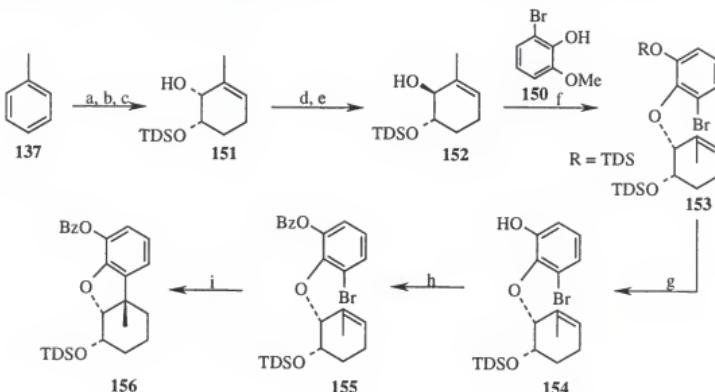


**Scheme 31** Conditions: a) NaH, sorbyl bromide; b) PPh<sub>3</sub>, THF; c) Ac<sub>2</sub>O, pyridine; d) 230° C, PhMe.

Alder approach towards the morphine skeleton in 1998. Unlike the first generation attempt, provisions were made for eventual closure of the D-ring by appending a nitrogen functionality from the quaternary carbon of the tricycle **149** (Scheme 31). During the cyclization of the triene, it was discovered that the stereochemistry of the methyl group at what would be C9 (morphine numbering) was indeed  $\beta$ -faced instead of  $\alpha$ -faced as had

been reported earlier. This led to the conclusion that the intramolecular Diels-Alder proceeded through an *exo* transition state.

In 1998, Hudlicky<sup>56</sup> and coworkers published a radical cyclization approach to the morphinan skeleton that represents the most advanced morphinan synthesized in the Hudlicky group. In the first generation of this radical approach, the focus was to

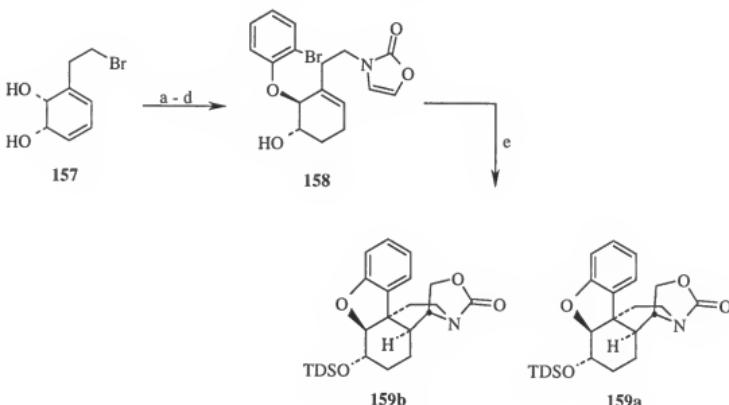


**Scheme 32** Conditions: a) JM109 (pDTG601); b) PAD, HOAc; c) THSCl, imidazole, DMF; d) BzOH, Bu<sub>3</sub>P, DEAD, THF; e) NaOMe, MeOH; f) **150**, Bu<sub>3</sub>P, DEAD, THF; g) H<sub>3</sub>O<sup>+</sup>; h) benzyl bromide, K<sub>2</sub>CO<sub>3</sub>, acetone; i) Bu<sub>3</sub>SnH, AIBN, toluene reflux.

achieve a tandem radical cyclization that would lead to the construction of the A, C, D, and O-rings of morphine (Scheme 32) with the correct stereochemistry at the chiral centers in a manner analogous to the Parker<sup>52</sup> synthesis but with different connectivity at the C9, C10 and C11 carbon atoms. The first step was to validate the tandem process with simple model studies. The initial model examined the feasibility of constructing the C12-C13 bond through a radical closure. To this regard bromoguaiacol **150** was synthesized in 4 steps starting from an enzymatic transformation with *P. putida* TG02C and used as a nucleophile in the second Mitsunobu inversion of the alcohol **152** also obtained through

an initial enzymatic step (Scheme 32). With ether **153** in hand the next steps involved protection of the phenol as the benzoate after cleavage of the labile thexyl group. Under radical conditions generated by  $\text{Bu}_3\text{SnH}$  and AIBN ether **155** was transformed to the tricyclic **156** with three of the five stereo centers in morphine set correctly.

A second model study (Scheme 33) to provide information about the relative

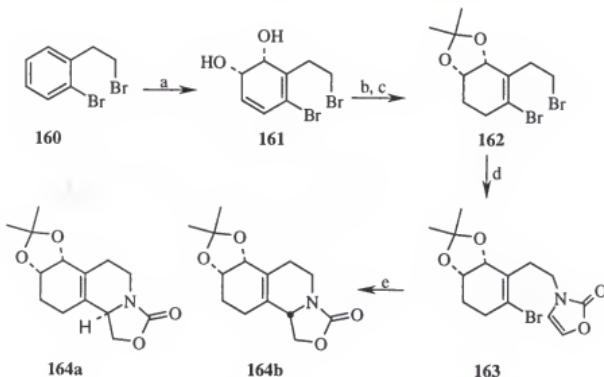


**Scheme 33** Conditions: a) PAD, HOAc; b) TBSOTf; c) *o*-bromophenol,  $\text{Bu}_3\text{P}$ , DEAD, THF; d) NaH, 2-oxazolidone; e)  $\text{Bu}_3\text{SnH}$ , AIBN, toluene reflux.

stereochemistry of the C9-C14 bond was designed using diene **157**, which was functionalized effectively in four steps into the oxazolone **158**. Under radical conditions pentacycle **159** was obtained in approximately 10% yield.  $^1\text{H}$  NMR analysis confirmed a *trans* relationship between the protons at C9 and C14 but it was difficult to ascertain the configuration of these chiral centers relative to C5 or C6 and so the product was assigned either as **159a** or **159b**.

With these two promising results Hudlicky and coworkers then focused on constructing the entire morphine skeleton. In the second-generation synthesis, *o*-bromo-

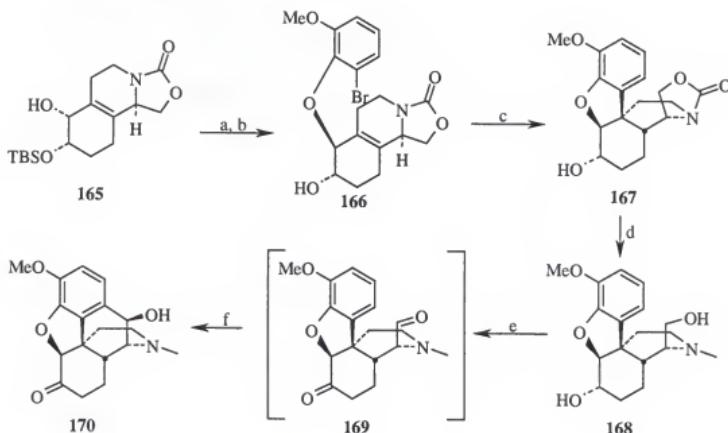
$\beta$ -bromoethylbenzene **160** was subjected to enzymatic conditions with the expectation that the larger bromoethyl group would direct the *cis*-dihydroxylation. This assumption proved to be correct because diol **161** was isolated from the fermentation broth using *E. coli* JM109 (pDTG601A). Diimide reduction of **161** followed by acetonide protection of the *cis*-diol moiety provided the dibromide **162**. Introduction of



**Scheme 34** Conditions: a) JM109 (pDTG601); b) PAD, HOAc; c) DMP, *p*TSA; d) 2-oxazolidone, NaH; e)  $\text{Bu}_3\text{SnH}$ , AIBN, benzene reflux.

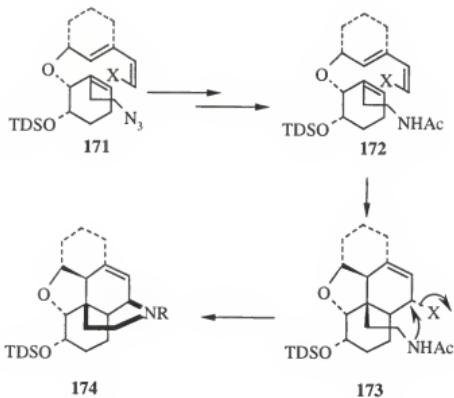
the oxazolidone gave **163**, which upon exposure to radical conditions gave a 2:1 mixture of octahydroisoquinolones **164a** and **164b** in favor of the isomer with an *epi*-C9 configuration (Scheme 34). The lack of stereo control was attributed to the negligible steric effect of the acetonide. Since the *epi*-isomer was in greater availability the decision was made to pursue the synthesis of *ent*-morphine. Mitsunobu inversion with bromoguaiacol generated the precursor for the second radical cyclization, ether **166**. Treatment with  $\text{Bu}_3\text{SnH}/\text{AIBN}$  gave pentacycle **167**. To complete the synthesis of the *ent*-morphinan, the silyl-protecting group was removed followed by reduction of the

oxazolidone to yield the alcohol **168**. A double Swern oxidation was utilized to convert **168** into the rather unstable ketoaldehyde **169**, which upon exposure to trifluoromethanesulfonic acid led to the formation of alcohol **170**, which contains the complete morphinan skeleton.



**Scheme 35** Conditions: a) **150**,  $\text{Bu}_3\text{P}$ , DEAD, THF; b) TBAF, THF; c)  $\text{Bu}_3\text{SnH}$ , AIBN, benzene reflux; d) DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ; e) oxalyl chloride, DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; f) TFA.

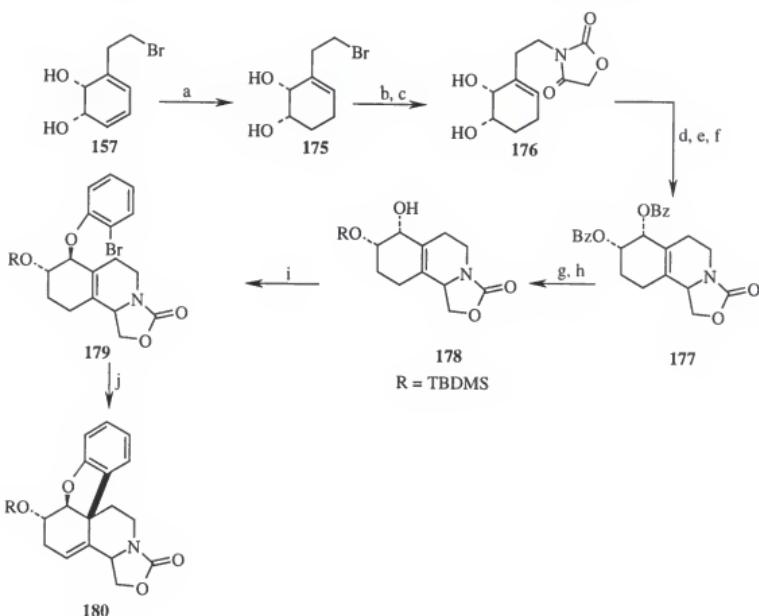
Currently<sup>57, 58</sup> a third generation approach using intramolecular Diels-Alder is being developed (Scheme 36). The major improvement in the third generation is the use of a (E, Z)-diene system as seen in **171** which will invariably lead to an inversion at the C9 (morphine numbering) stereocenter preceding the formation of compounds of the type **173**. Using a nucleophilic displacement by the nitrogen tether onto the leaving group would form B-, C-, D-, and O-rings with correct stereochemistry in **174**.



Scheme 36

Another noteworthy approach to the morphinan skeleton was recently published by Hudlicky and coworkers.<sup>59</sup> It involves a rare Heck cyclization to yield an advanced pentacyclic precursor of morphine. Biooxidation of (2-bromoethyl)-benzene **157**, with *Escherichia coli* JM109 (pDT601) followed by reduction of the less hindered double bond with diimide yielded diol **175** in 80% yield (Scheme 37). The next step involved protection of the two diol moieties as the benzoate. This was followed by displacement of the bromine by oxazolidine-2,4-dione to afford the dibenzoate **176**. After reduction of the more reactive amide carbonyl with NaBH<sub>4</sub>, N-acyliminium ion-olefin cyclization and subsequent elimination of the alkyl chloride afforded the tricycle **177**. This was followed by deprotection of the benzoate groups and subsequent selective protection of the

homoallylic hydroxyl group as the TBDMS ether. Using Mitsunobu protocol the

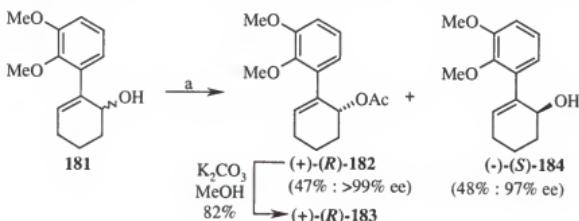


**Scheme 37** Conditions: a) *E. coli* JM109 (pDTG601); b) PAD, AcOH, MeOH; c) PhCO<sub>2</sub>H, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; d) Oxazolidine, tetramethylguanidine, THF, reflux; e) NABH<sub>4</sub>, MeOH; f) AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; g) DBU, DMSO, reflux; h) LiOH, MeOH; i) TBDMSCl, imidazole, DMF; j) Bu<sub>3</sub>P, DEAD, bromoguaiacol, THF; k) Pd(PPh<sub>3</sub>)<sub>4</sub>, proton sponge, toluene, reflux.

unprotected alcohol was converted into the bromoguaiacol derivative to give intermediate 179. Heck cyclization of the tetrasubstituted olefin yielded the tetracycle 180 as the only identifiable product.

In a recent publication in *Organic Letters*,<sup>60</sup> Ogasawara and co-worker undertook a rather elaborate approach to the morphine skeleton that deserves mention because of their clever approach to the construction of the C14 stereocenter correctly and also their

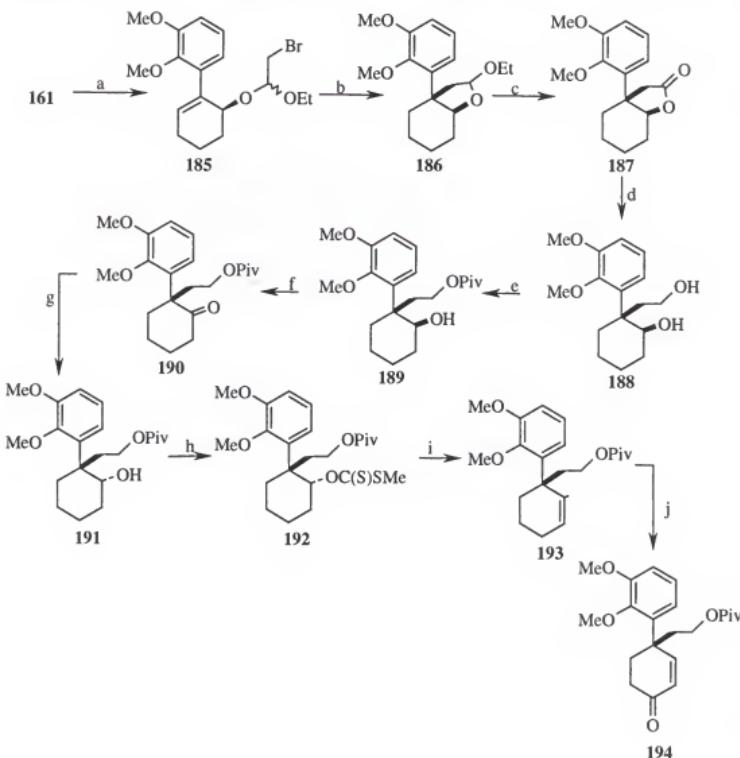
construction of the C9-C10 bridge. Starting from a mixture of the alcohol **181** they



**Scheme 38** Conditions: a) vinyl acetate, lipase PS, Bu'OMe, 37 °C.

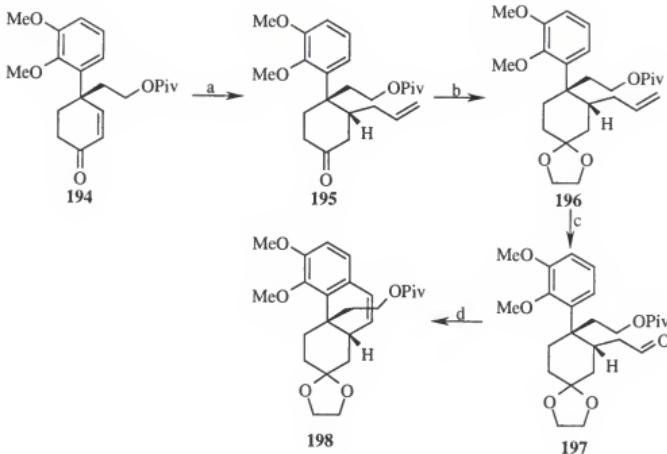
are able to obtain the pure *S*-isomer through an optimized pathway<sup>61</sup> (Scheme 38) using vinyl acetate. Even though this synthesis was undertaken with the racemic mixture, the use of isomer **184** is projected for a future synthesis of natural morphine. Starting from the mixture of alcohols **181** they synthesized the bromoacetal **185** as a mixture by utilizing ethyl vinyl ether in the presence of NBS (Scheme 39). Under radical cyclization conditions, they were able to obtain the cyclized product in moderate yields. The authors attributed this to the steric hindrance caused by the methoxy group in the 2-position of the aromatic ring. The cyclized product **186** was converted in 3 steps into the ketone **190**. Reduction of the ketone with NaBH<sub>4</sub> yielded the alcohol **191** diastereoselectively. This result might be due to prior coordination of the borohydride reagent to the pivaloyl moiety, which results in hydride delivery to the β-face of the molecule. The xanthate **192** (Scheme 39) obtained from the alcohol **191** was then thermolyzed to afford the cyclohexene derivative **193** in 81% yield. Allylic oxidation of **193** using chromium

trioxide and 3,5-dimethylpyrazole complex in  $\text{CH}_2\text{Cl}_2$  afforded the enone **194**. Using



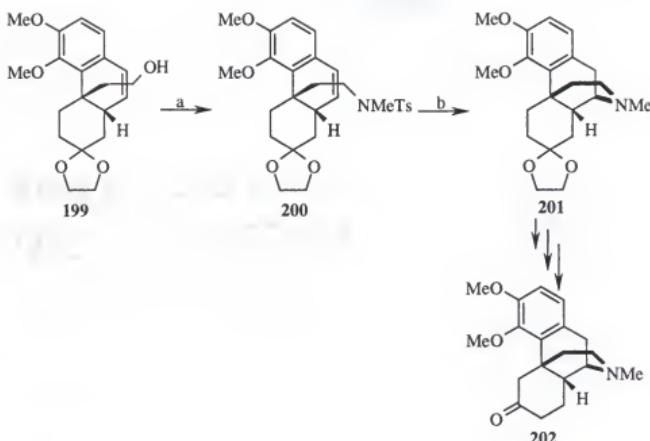
**Scheme 39** Conditions: a) EVE, NBS,  $\text{Et}_2\text{O}$ . b)  $\text{Bu}_3\text{SnH}$ , AIBN (cat.), benzene. c) *m*-CPBA,  $\text{BF}_3\cdot\text{OEt}_2$ . d)  $\text{LiAlH}_4$ , THF. e) Piv-Cl, pyridine. f) PDC,  $\text{CH}_2\text{Cl}_2$ . g)  $\text{NaBH}_4$ ,  $i\text{PrOH}$ . h)  $\text{MeI}$ ,  $\text{CS}_2$ ,  $\text{NaH}$ . i)  $\text{o-C}_6\text{H}_4\text{Cl}_2$ , reflux. j)  $\text{CrO}_3\cdot 3,5\text{-(Me)}_2\text{pyrazole}$ .

Sakurai conditions allyl functionality was introduced at the C14 center (morphine numbering) by treatment of **194** with allytrimethylsilane (Scheme 40) in the presence of titanium (IV) chloride. Ketone **195** was then transformed into the ketal **196** followed by



**Scheme 40** Conditions: a) allylTMS, TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78° C. b) (CH<sub>2</sub>OH)<sub>2</sub>, *p*-TsOH, benzene, reflux. c) OsO<sub>4</sub> (cat.), NaIO<sub>4</sub>. d) (CH<sub>2</sub>OH)<sub>2</sub>, *p*-TsOH, benzene, reflux.

reductive cleavage of the olefin in **196** to afford the aldehyde **197**. Upon reflux in benzene in the presence of ethylene glycol and catalytic amounts of *p*-toluenesulfonic acid, the hydrophenanthrene **198** was obtained in 85% yield. Construction of the D-ring was achieved using Parker conditions, which involved deprotection of the pivaloyl group followed by Mitsunobu (Scheme 41) coupling of the free alcohol **199** with N-methyl-*p*-toluenesulfonylamide to give the tosylate **200**. Treatment of the tosylate with sodium naphthalenide afforded the morphinan **201** in 89% yield via concomitant detosylation followed by regioselective cyclization. Morphinan **201** was then converted in 3 steps to the morphinan **202**, which is the *O*-methylated analogue of dihydrothebainone **35** (page 14).

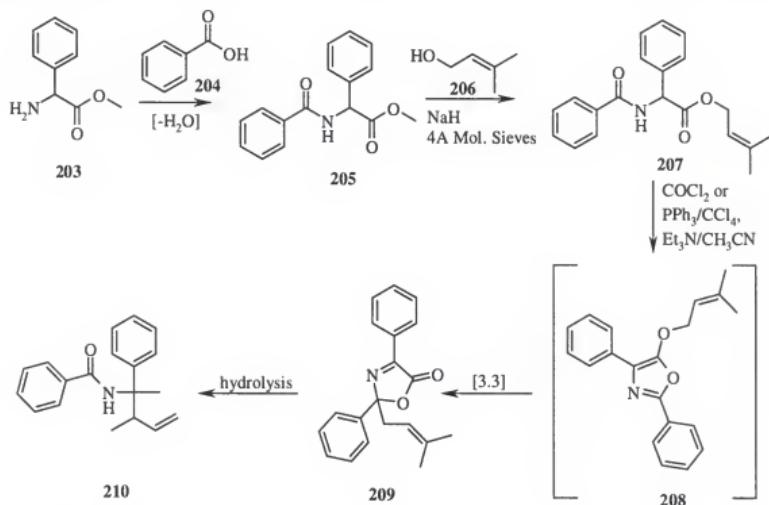


**Scheme 41** Conditions: a) LiAlH<sub>4</sub>, MeNHTs, Bu<sub>3</sub>P, DPAP. b) Sodium naphthalenide, THF, -30° C.

#### Chelated Enolate Claisen Rearrangements

In 1977 Wolfgang Steglich<sup>62, 63</sup> reported the synthesis of a series of amino acids utilizing a Claisen rearrangement. This was the first time the Claisen rearrangement had been extended to the synthesis of this important class of compounds. Steglich and co-workers first synthesized N-benzoyl  $\alpha$ -amino acid esters with a general structure such as 205. After transesterification with the allyl alcohol 206, they then observed that under dehydration conditions oxazoles were formed. The oxazoles thus formed concomitantly rearranged without isolation to form oxazolones 209 (Scheme 41). Under conditions of hydrolysis they observed the formation of  $\beta$ -amino acid with the general structure of 210 in yields up to 95%. The oxazole intermediate 208 can be seen as a trapped enolate

whose geometry is fixed by virtue of being in the five membered oxazole ring. This



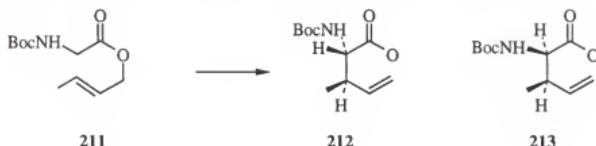
Scheme 41

important aspect of the reaction meant that the sigmatropic rearrangement could proceed with stereoselectivity. Unfortunately when the substituent  $\alpha$ - to the nitrogen is hydrogen there is epimerization at that center leading to a non-stereoselective rearrangement.

Paul Bartlett<sup>64</sup> in 1982 decided to investigate the work done earlier by Steglich. His goal was to compare these conditions to the Ireland Claisen<sup>65</sup> rearrangement conditions. Also important was the utilization of this reaction in the synthesis of  $\gamma,\delta$ -unsaturated amino acids. He also wanted to study the stereochemical influence, if any of the  $\alpha$ -substituent in the Claisen rearrangement. Deprotonation Conditions: Bartlett and coworkers used 2.1 equivalents of LDA to effect enolization. They found that shorter (2.5 min) or longer (40 min) enolate generation times had no significant influence on yield or

stereoselectivity. Also the use of TBDMS chloride instead TMS chloride as the silylating agent did not increase yield or stereoselectivity. Reaction in a less polar solvent (ether) proceeded with a slight increase the stereoselectivity but led to a decreased yield.

**Table 1.** Influence of Conditions on Rearrangement of Amino Esters.

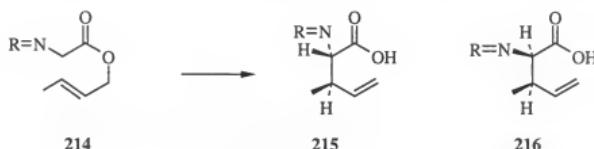


Conditions	Yield / %	Ratio 212/213
*Standard	60-65	9
Ether	45	10
20% HMPT/THF solvent	51	4
KDA	0	
1.1 equiv of MgCl <sub>2</sub>	42	10

\*Deprotonation at -75°C with 2.1 equiv. of lithium isopropylcyclohexylamide or lithium diisopropyl amide; silylation with Me<sub>3</sub>SiCl after 10 min; warming to reflux for 1h; hydrolysis of silyl ester.

Contrastingly the use of HMPA and TMEDA, which are highly dissociating systems as co-solvents resulted in both lower yield and lower stereoselectivity (Table 1). The use of a lewis acid (MgCl<sub>2</sub>) also slightly increased stereoselectivity but led to a lower overall yield. The result of this study is in concurrence with the accepted principle of an *E*-enolate geometry and a chair-like transition state for aliphatic substrates. He proposed that coordination of the counter ion between the carbonyl oxygen and the nitrogen anion is at least partly responsible for the *E*-enolate geometry.

Influence of N-Protecting Groups: A variety of N-protecting groups were explored (Table 2) with varying yields and stereoselectivity. Overall the Boc- protecting

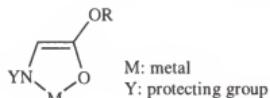
**Table 2.** Effect of *N*-Protecting Groups on Rearrangement of *trans* ButenylGlycines

R	yield / %	Ratio 215/216
1. Boc	60-65	9
2. Cbz	65	4
3. Bz	65	5.4
4. CF <sub>3</sub> CO	58	1.5
5. Phthaloyl	0	
6. Et <sub>2</sub>	0	

group gave the best results. The reduced stereoselectivity with the trifluoroacetyl derivative (Entry 4) was explained by reduced importance of the chelation effect due to the increased acidity of the nitrogen. The inability to obtain products in the case of the *N*-phthaloyl and *N,N*-diethyl analogues was attributed to the lack of an extended conjugated system for nitrogen-substituted enolate stabilization.

Uli Kazmaier<sup>66-77</sup> in 1994 published an article about a remarkable variation to the classical enolate Claisen rearrangement that would revolutionalize the synthesis of both natural and unnatural amino acids. It had already been established by Steglich<sup>62, 63</sup> that enolizable amino acids could undergo rearrangement with moderate to good stereoselectivity if the enolate geometry was fixed either in the form of an oxazole ring or

constricted due to chelation with the counter ion. While Bartlett<sup>64</sup> had always converted the enolate into the silylketene acetal, Kazmaier discovered that by allowing the chelated enolates (Figure 1) to simply warm up from -78° C to about -15° C resulted in

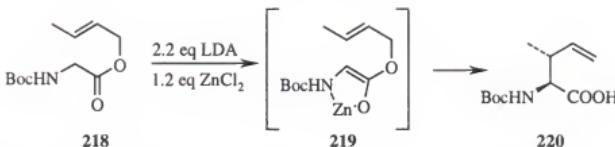


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**Figure 1.** Nature of Chelated Enolate in Kazmaier Claisen Rearrangement.

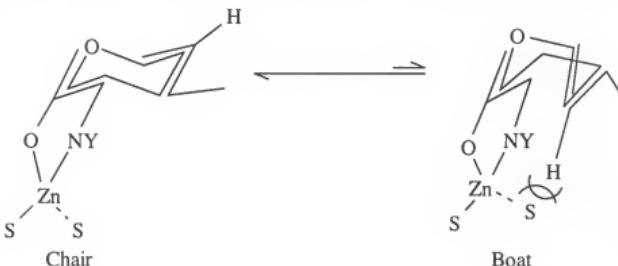
rearranged products in excellent yields and also high diastereoselectivity. The chelated enolates had several advantages. Since the chelated enolates are significantly more stable than the corresponding non-chelated lithium enolates, they can be warmed to room temperature without decomposition and side reactions such as ketene formation via elimination can be suppressed. Secondly because of the fixed enolate geometry due to chelation, the reactions proceed with high diastereoselectivity. Due to the inherent flexibility of this chemistry, many variations of protective groups Y (Figure 1) can be used. Varying the metal M used can also modify the selectivity and reactivity of the reaction. Since the coordination sphere of a metal ion is not saturated in a bidentate enolate system, this allows for additional coordination with external ligands. Lastly transformation of the high-energy ester enolate into a chelate-bridged stabilized carboxylate provides a good driving force for the reaction.

When this reaction was applied to acyclic allylic esters the results obtained confirmed a preferred chair-like transition state. Even though different Lewis acids were utilized, ZnCl<sub>2</sub> produced the best results (Scheme 42). The formation of the *syn* product



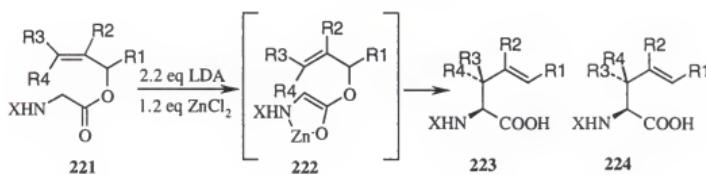
Scheme 42

is explained by a preferential rearrangement through the chair-like transition state (Figure 2), which avoids the steric interactions between the pseudoaxial hydrogen and



**Figure 2.** Chair vs boat transition states in the Kazmaier Claisen Rearrangement of acyclic substrates.

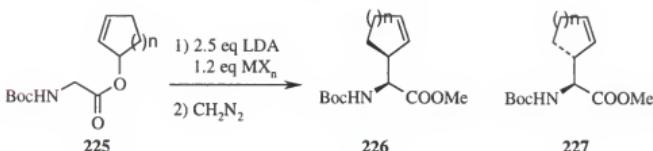
the chelate complex in the boat transition state. The results obtained in the acyclic series of experiments are summarized in Table 3, which details the influence of substituents at the double bond, the olefin configuration and the different nitrogen-protecting groups as related to the yield and diastereoselectivity of the rearrangement products. All the substituted allyl esters displayed high diastereoselectivity where the formation of *syn* products from trans substituted esters and anti products from *cis* substituted esters were favored.

**Table 3.** Results from Acyclic Kazmaier Claisen Rearrangement

X [a]	R1	R2	R3	R4 [b]	Yield	Diastereomer ratio (±)-223: (±)-224	
1	Z	H	H	H	88	-	
2	Z	H	CH <sub>3</sub>	H	78	-	
3	Z	H	H	C <sub>3</sub> H <sub>7</sub>	76	95:5	
4	Z	CH <sub>3</sub>	H	CH <sub>3</sub>	88	93:7	
5	Z	C <sub>2</sub> H <sub>5</sub>	H	CH <sub>3</sub>	98	95:5	
6	Z	C <sub>2</sub> H <sub>5</sub>	H	H	C <sub>4</sub> H <sub>9</sub>	73	95:5
7	Boc	CH <sub>3</sub>	H	CH <sub>3</sub>	H	84	96:4
8	Boc	H	H	C <sub>3</sub> H <sub>7</sub>	H	78	96:4
9	TFA	H	H	C <sub>3</sub> H <sub>7</sub>	H	79	95:5
10	TFA	C <sub>2</sub> H <sub>5</sub>	H	H	C <sub>4</sub> H <sub>9</sub>	65	94:6
11	Z	H	H	H	D	75	98.5:1.5

[a] Z = benzyloxycarbonyl, Boc = tert-butoxycarbonyl, TFA = trifluoroacetyl  
 [b] D = tert-butylidiphenylsilyl

Due to the excellent results obtained with the acyclic substrates, the chemistry was applied to cycloalkenyl glycinate (Scheme 43). These substrates were of particular interest because their rearrangement would yield  $\gamma,\delta$ -unsaturated amino acids, a class of compounds with high activity as enzyme inhibitors. Indeed it had been previously postulated that cyclic allylic esters prefer to rearrange via a *boat-like* transition state. Kazmaier and coworkers investigated the effect of ring size as well as the metal salt used for chelation of the ester enolate (Table 4). As predicted, with the cyclic allylic esters the *syn*-product is preferred and the best results with respect to yield and stereoselectivity



Scheme 43

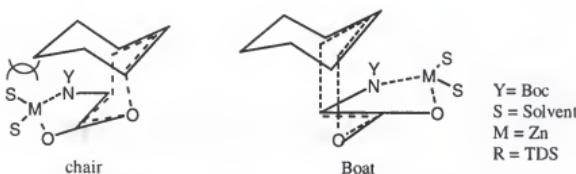
are obtained with cyclohexenyl glycines ( $n = 2$ ). All the metal salts used gave good product yields in the cyclohexenyl case ( $n = 2$ ). The crude amino acids obtained were directly converted into the corresponding methyl esters using diazomethane. The best results were obtained with zinc chloride and are summarized in Table 4.

Table 4. Results from Rearrangement with Zinc Chloride.

n	% Yield	Ratio 226:227
1	79	80 : 20
2	83	90 : 10
3	73	92 : 8
4	57	86 : 14

It was noted during this study that homologous cycloheptenyl substrates ( $n = 3$ ) showed similar degrees of diastereoselectivity as in the cyclohexenyl case. However increase in ring size to the more flexible cyclooctenyl case ( $n = 4$ ) resulted in decrease in selectivity. Also noteworthy was the fact that diastereoselectivity in the cyclopentenyl case ( $n = 1$ ) was lower than that observed for the cyclohexenyl and cycloheptenyl cases respectively. The product formation as well as the diastereoselectivities observed for the six and seven membered esters were explained by rearrangement through a boat-like transition state,<sup>67</sup>

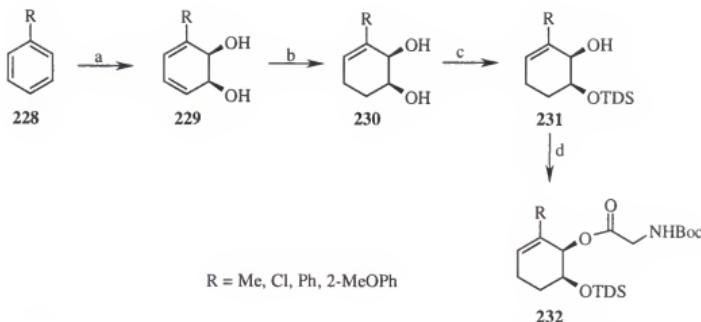
which minimizes the steric interactions between the cycloalkenyl ring and the solvated chelating metal (Figure 3).



**Figure 3.** Chair vs boat transition states in the Kazmaier Claisen Rearrangement of cyclic substrates.

In summary Kazmaier has successfully demonstrated the utility of his variation of the classic enolate Claisen rearrangement. The chelated ester enolate rearrangement is not partial to acyclic substrates but can also be practical for cyclic substrates. High diastereoselectivity and excellent yields are observed for the rearrangements, which proceed via a boat-like transition state for cyclic esters and a chair-like transition state for acyclic esters.

In 1997 Hudlicky<sup>78</sup> and coworkers applied the Kazmaier chelated enolate rearrangement to their chemoenzymatic approach to morphine. Model studies to obtain optimum reaction conditions were undertaken on compounds of type 232. These glycinate were obtained first by direct oxidation of the aromatic precursor by either the mutant strain *Psuedomonas putida* F39/D or the more potent recombinant organism *Escherichia coli* JM109(pDTG601A) to render the diene-diols of type 229. After diimide (potassium azodicarboxylate) reduction of the less hindered double bond, the distal

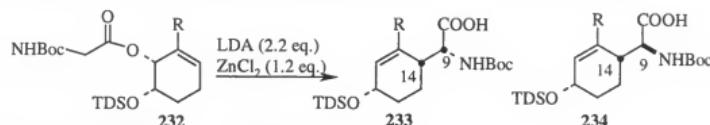


**Scheme 44.** Conditions: a) Toluene dioxygenase expressed in *Pseudomonas putida* F39/D ( $R = \text{Me}$ ; 3.5 g/L) or *Escherichia coli* JM109 (pDT601A) ( $R = \text{Cl}$ ; 10.0 g/L), ( $R = \text{Ph}$ ; 3.0 g/L), ( $R = \text{MeOPh}$ ; 2.5 g/L). b) PAD, HOAc, MeOH,  $0^\circ\text{C} \rightarrow \text{rt}$ , 12h., 85 – 95%. c) TDSCI, imidazole, DMF,  $-5^\circ\text{C}$ , 8h., 80 – 90%. d) Boc-Gly, DCC, DMAP,  $\text{CH}_2\text{Cl}_2$ , 24 – 48h., 75 – 90%.

hydroxyl group was then protected as the THS-ether. DCC coupling protocol was used to convert the proximal hydroxyl group into the Boc- protected glycyl derivative **232** (Scheme 44).

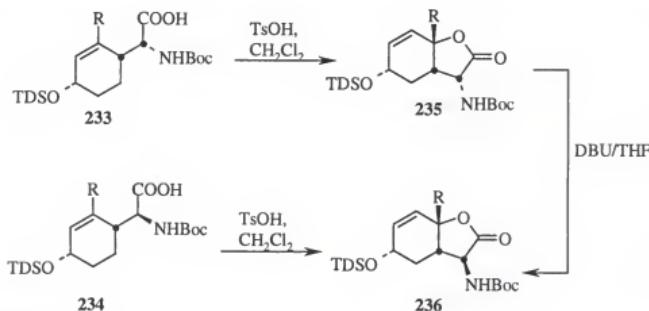
The glycinate ( $R = \text{Me}$ , Cl, Ph, 2-MeOPh) served as the substrates for the first Claisen study. The results obtained were quite promising in term of yield. All the glycinate underwent rearrangement under the Kazmaier conditions with yields ranging from 25 – 90%. Surprisingly the configuration of the major product of the rearrangement was opposite to that expected (Table 5). Due to the fixed enolate geometry, which is a result of the formation of the chelate, the only variable would be the predominance of one transition state over the other. In this case the chair transition state clearly predominates leading to the product ratios observed.

**Table 5.** Ratio of C9 Epimers for Kazmaier Claisen Rearrangement of glycinate



R	233	234	Overall yield
Ph	75%	25%	80%
CH <sub>3</sub>	75%	25%	90%
Cl	90%	10%	25%
2-MeOPh	50%	50%	75%

Due to the lack of control of stereoselectivity, the authors considered epimerization of the lactones resultant from treatment of the epimeric amino acids with tosic acid (Scheme 45). They reasoned that since the bulky protected amino acid was

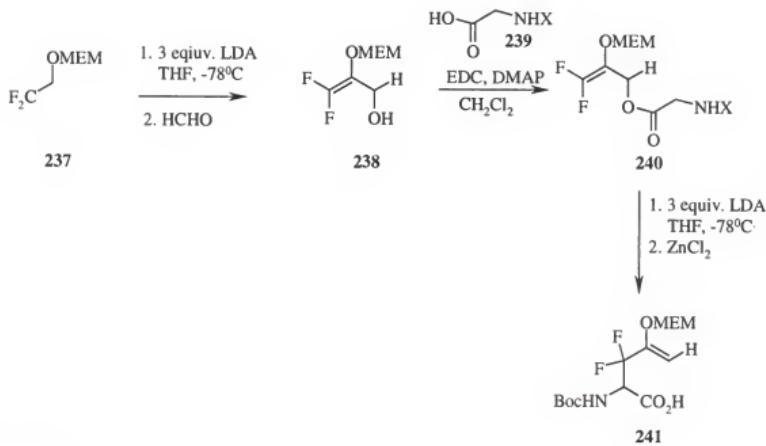


**Scheme 45**

more accessible in the wrong isomer (situated on the concave face of the bicyclic molecule), it could be effectively epimerized to the more stable isomer. Hence after treatment with DBU in THF for 37h they were able to achieve an 80% epimerization of

**235** to give the isomer with correct stereochemistry at C9 and C14 (morphine numbering).

Inspired by the work of Kazmaier and the subsequent application of this chemistry by Hudlicky and co-workers<sup>78,79</sup> in their approach to the morphine skeleton, Percy<sup>79</sup> and co-workers investigated the possibility of generating  $\gamma$ -oxo- $\beta,\beta$ -difluorinated amino acids by chelated [3.3]-sigmatropic rearrangement of protected glycinate esters of readily available difluoroallylic alcohols. This type of rearrangement had the potential to produce amino acids having a CF<sub>2</sub> center  $\alpha$  to a carbonyl functionality through release of the masked carbonyl group (Scheme 46).



Scheme 46

The synthesis started with difluoroallylic alcohol **238**, which was converted into the glycyl ester **240** under DCC coupling conditions. The glycinate was then subjected to modified Kazmaier Claisen condition which involves the use of 3 equivalents of LDA added in a reverse addition order to that proposed by Kazmaier (the Lewis acid is added

after generation of the enolate with LDA). After acidic workup the only isolated product was the rearranged acid **241**.

In summary the synthesis of morphine has resulted in ingenious strategies by different research groups over the years to tackle this small yet challenging molecule. While the focus of the various syntheses has been synthesis of the target, the chemistry generated by this pursuit and its application to alkaloid chemistry is the legacy of morphine synthesis. Starting from Gates' <sup>15, 16</sup> synthesis to the latest synthesis by Mulzer<sup>21-25</sup> it is fascinating to see the many different synthetic pathways that have been employed in morphine synthesis. Sigmatropic rearrangements have played a small yet important role in morphine synthesis. The syntheses by Parsons,<sup>20</sup> Rapoport<sup>50</sup> and Mulzer<sup>21-25</sup> effectively used sigmatropic rearrangements to establish the C13 quaternary center of morphine.

The chelated enolate Claisen Rearrangement had modest beginnings from Steglich<sup>62, 63</sup> and coworkers and later Bartlett<sup>64</sup> and coworkers. The idea was greatly improved by Kazmaier<sup>66-77</sup> and coworkers who have developed it into one of the more powerful tools in amino acid chemistry.

The next chapter of this dissertation will discuss a chemoenzymatic approach to the synthesis of the morphine skeleton. This approach uses a disconnection of the morphine molecule that is unlike any of the preceding syntheses. More importantly, it utilizes a sigmatropic rearrangement, the Chelated Enolate Claisen rearrangement (Kazmaier Claisen) to establish control of C9 and C14 stereocenters of morphine in addition to attempting to establish the C13 quaternary center. Additionally the synthesis uses an enzymatic step, which is capable of converting cheap readily available aromatic

precursors into either catechols (A-ring of morphine) or cyclohexadiene diols (C-ring of morphine). With all these factors combined, the chemoenzymatic approach becomes an attractive route to the morphinan skeleton.

In 1968 as a result of studies conducted by David T. Gibson<sup>87</sup> on the microbial oxidation of aromatic hydrocarbons by soil bacteria, the first stable *cis*-diol was isolated. The organism responsible for this transformation was a mutant strain of the bacteria *Pseudomonas putida* (F1) and was designated *Pseudomonas putida* (F39/D). This strain was devoid of the *cis*-diol dehydrogenase enzyme hence only produced the *cis*-diene diol. The use of these diols as synthons was initiated in the late 1980's with work done by Ley<sup>88</sup> and coworkers who achieved a racemic synthesis of pinitol from *meso-cis*-diols derived from benzene. Since then, one of the leading researchers in this area of chemistry has been Hudlicky who has been able to utilize the *cis*-diene-diols as chiral synthons<sup>86</sup> in the synthesis of a wide variety of compounds.

In 1988, in the first publication by Hudlicky and co-workers in this area, the idea of Claisen rearrangements of the allylic alcohol unit of the *cis*-diols was proposed. This idea was actually reduced to practice in 1997 and thus began the initial studies that featured the Claisen rearrangement as a key step in the chemoenzymatic approach to the morphine skeleton.<sup>86</sup>

In the first generation of this approach, conditions for a suitable Claisen rearrangement that would lead to the transfer of stereochemical information inherent in the cyclohexadiene-diols were investigated. The Kazmaier-Claisen rearrangement offered the best conditions for this purpose. The goal was to synthesize  $\beta$ -amino acids of different complexity bearing chiral side chains. Eventually such compounds would

contain the correct stereochemistry at the C9 and C14 (morphine numbering) centers of morphine.

In the initial model studies, as reviewed in the historical chapter it was discovered that even though the Claisen rearrangements proceeded with low stereoselectivity, there was the potential to achieve complete control of the C9, C14 stereocenters through equilibration of isomers. Efforts in the initial stages of this approach were also directed at finding efficient ways of obtaining the bicyclic skeleton. One of the opportunities for construction of this bicycle was through direct enzymatic dihydroxylation of substituted biphenyls. Indeed when selected biphenyls were subjected to biooxidation conditions, the resultant diene diols were obtained.<sup>78</sup> Unfortunately it became apparent that as the degree of oxidation in the substrate increased, the yield for the enzymatic process decreased considerably probably as a result of poisoning of the bacteria by the oxygenated substrate.

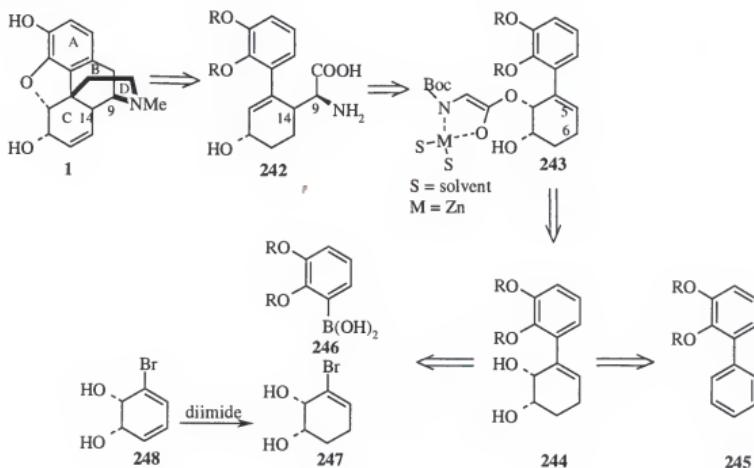
This dissertation will focus on the progress made in the second generation of the chemoenzymatic approach to morphine. The discussion will address how control of the C9 and C14 centers of morphine was achieved through the use of the Kazmaier-Claisen rearrangement and epimerization. It will also give an account of the progress made toward a formal total synthesis of morphine *via* Overman's intermediate. In addition some applications in the field of matrix metallo proteinase inhibitors, compounds that are connected to morphinan intermediates through common structural elements will be discussed. Finally recent advances in the chemoenzymatic approach to morphine will also be discussed.

CHAPTER 3  
RESULTS AND DISCUSSION

Introduction

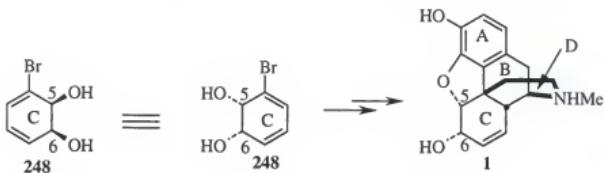
The structural complexity of the morphine molecule has prompted many innovative routes to the morphinan skeleton as was detailed in the first chapter. The synthetic design utilized in the chemoenzymatic synthesis of the morphinan skeleton, makes it a very attractive route to the morphine molecule. Retrosynthetically, the approach is directed toward the target through the intermediate  $\beta$ -cyclohexenyl amino acid **242**. The amino acid could be obtained through a Claisen rearrangement of the Xxx

**Scheme 47**



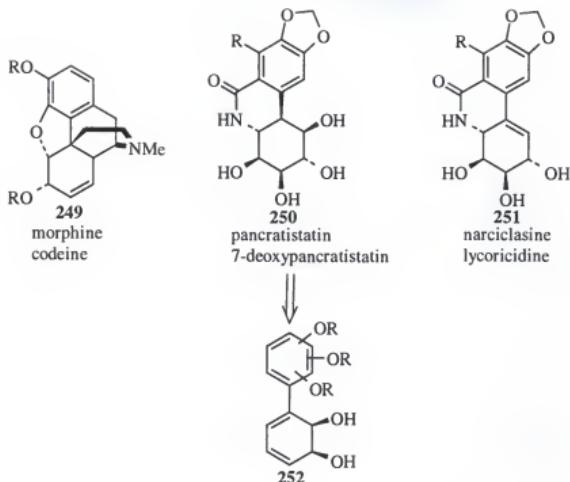
glycinate ester **243** which could be synthesized from the biphenyl diol derivative **244**. This synthon is available either from direct biooxidation of the biphenyl precursor **245** or through the coupling reaction between the aromatic boronic acid **246** and diol **247** derived from diimide reduction of the *cis*-diene diol **248** (Scheme 47).

The retrosynthetic strategy outlined above uses remarkable design elements that deserve mention. 1) The C-ring of morphine can essentially be described as a cyclohexenyl *cis*-diol unit. This moiety can be recognized in the structure of the chiral



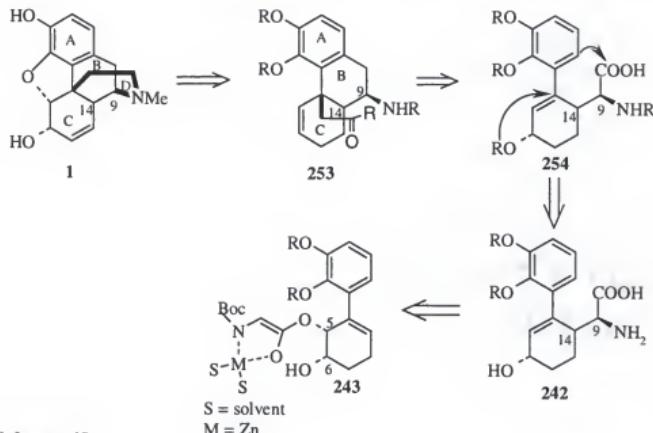
**Scheme 48**

*cis*-cyclohexadiene diol **248** with the correct absolute stereochemistry at C5 and C6 set as a result of the enzymatic transformation (Scheme 48). 2) The approach capitalizes on the recognition that the main backbone of the morphine skeleton consists of an oxidized biphenyl unit **252** (Figure 4). This structural component, namely **244** (Scheme 47), is also present in various alkaloids like pancratistatin the synthesis of which is being pursued in the Hudlicky group. This unit could be obtained as outlined above either through direct biooxidation of a biphenyl precursor or through the coupling of an aromatic boronic acid with *cis*-cyclohexadiene diol (Scheme 47). 3) The allylic alcohol unit present in diol **244** (Scheme 47) allows for the introduction of the amino acid side chain into the molecule through a Claisen rearrangement. 4) Finally the C13 quaternary center could be



**Figure 4.** Synthetic targets with oxidized biphenyl unit.

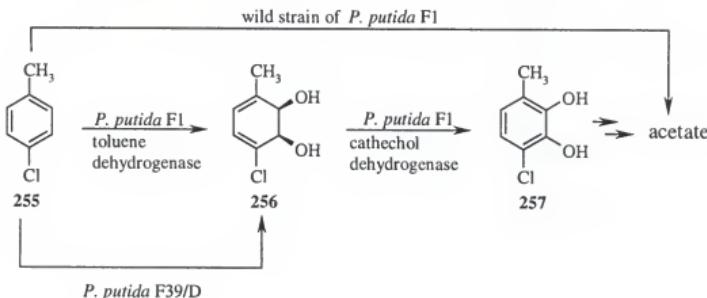
established by utilizing the allylic alcohol moiety present in intermediate **254** via a



**Scheme 49**

second Claisen rearrangement. The amino acid **254** is also set up for closure of the C10-C11 using a Friedel-Craft reaction after conversion of the acid into the aldehyde or the acid chloride. Before the discussion proceeds into the actual execution of the approach, a brief history about the development of the chemistry of enzymatic dihydroxylations would be in order.

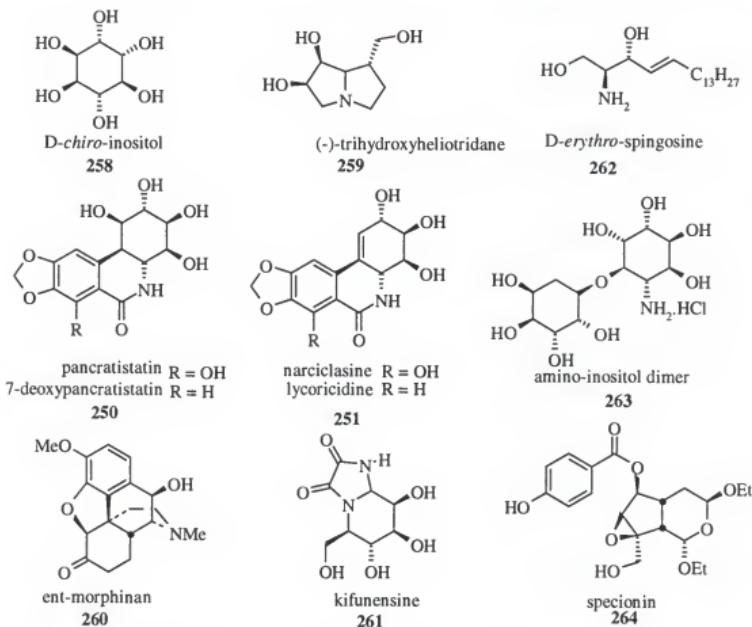
In 1968 as a result of studies conducted by David T. Gibson<sup>87</sup> on the microbial oxidation of aromatic hydrocarbons by soil bacteria, the first stable *cis*-diol **256** was



Scheme 50

isolated. The organism responsible for this transformation was a mutant strain of the bacteria *Pseudomonas putida* (F1) and was designated *Pseudomonas putida* (F39/D). This strain was devoid of the *cis*-diol dehydrogenase enzyme hence only produced the *cis*-diene diol **256** (Scheme 50). The use of these diols as synthons was initiated in the late 1980's with work done by Ley<sup>88</sup> and coworkers who achieved a racemic synthesis of pinitol from *meso-cis*-diols derived from benzene. Since then, one of the leading researchers in this area of chemistry has been Hudlicky who has been able to utilize the *cis*-diene-diols as chiral synthons<sup>86</sup> in the synthesis of a wide variety of compounds (Figure 5).

In 1988, in the first publication by Hudlicky and co-workers in this area, the idea of Claisen rearrangements of the allylic alcohol unit of the *cis*-diols was proposed. This idea was actually reduced to practice in 1997 (pg 49-52, historical section) and thus began the initial studies that featured the Claisen rearrangement as a key step in the



**Figure 5.** (Examples of Targets Synthesized from *cis*-diols)

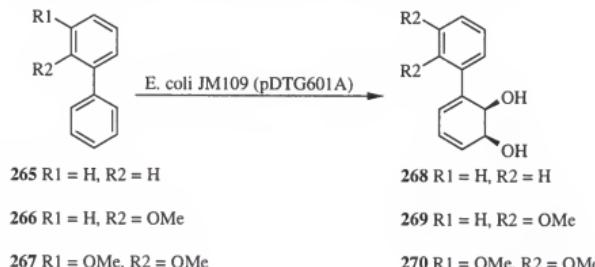
chemoenzymatic approach to the morphine skeleton.<sup>86</sup>

In the first generation of this approach, conditions for a suitable Claisen rearrangement that would lead to the transfer of stereochemical information inherent in the cyclohexadiene-diols were investigated. The Kazmaier-Claisen rearrangement offered the best conditions for this purpose. The goal was to synthesize  $\beta$ -amino acids of

different complexity bearing chiral side chains. Eventually such compounds would contain the correct stereochemistry at the C9 and C14 (morphine numbering) centers of morphine.

In the initial model studies, as reviewed in the historical chapter (pages 49-51), it was discovered that even though the Claisen rearrangements proceeded with low stereoselectivity, there was the potential to achieve complete control of the C9, C14 stereocenters through equilibration of isomers. Efforts in the initial stages of this approach were also directed at finding efficient ways of obtaining the bicyclic skeleton 252 (Figure 4). One of the opportunities for construction of this bicycle was through direct enzymatic dihydroxylation of substituted biphenyls. Indeed when selected biphenyls were subjected to biooxidation conditions, the resultant diene diols were obtained.<sup>78</sup> Unfortunately it became apparent that as the degree of oxidation in the substrate increased, the yield for the enzymatic process decreased considerably probably

**Table 6.** Results from Biooxidation of substituted biphenyls.



Substrate	Yield (g/l)
265	3.0
266	2.5
267	0.8

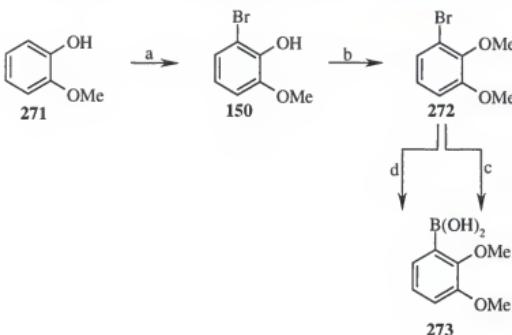
as a result of poisoning of the bacteria by the oxygenated substrate (Table 6). The low yields that accompanied the biooxidation of **267** to diol **270** the morphine precursor prompted us to seek other ways of constructing this bicyclic skeleton with the intent of functionalizing it appropriately into the morphinan skeleton.

This dissertation will focus on the progress made in the second generation of the chemoenzymatic approach to morphine. The discussion will address how control of the C9 and C14 centers of morphine was achieved through the use of the Kazmaier-Claisen rearrangement and epimerization. It will also give an account of the progress made toward a formal total synthesis of morphine *via* Overman's intermediate. In addition some applications in the field of matrix metallo proteinase inhibitors, compounds that are connected to morphinan intermediates through common structural elements will be discussed. Finally recent advances in the chemoenzymatic approach to morphine will also be discussed.

#### First Generation Synthesis- Control of C9 and C14 Stereocenters of Morphine

The first few steps in the synthesis focused on the Suzuki Coupling protocol in the synthesis of biphenyl diol derivative **270** (Table 6) which would then be functionalized into a glycinate ester. Starting from guaiacol (**271**), a known compound, which is not commercially available, we employed a procedure used by Hoshino<sup>83</sup> and coworkers in their synthesis of lycoramine. It involves first, the generation of a tert- butylamine bromine complex by addition of bromine to the amine at -68° C for a 24 - 48 hour period. After formation of the complex, which is the actual brominating agent, the reaction mixture is cooled back to -78° C at which time a solution of guaiacol dissolved in minimum amount of methylene chloride is added dropwise (Scheme 51). The reaction

typically gives a 50-60 % yield of bromogiuacol (**150**) in addition to two other

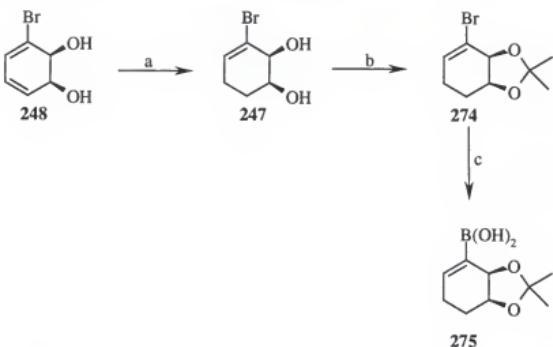


**Scheme 51.** Conditions: a)  $\text{Br}_2$ , *tert*-butylamine, toluene,  $-78^\circ \text{ C}$ , 60-62 %; b)  $\text{MeI}$ ,  $\text{K}_2\text{CO}_3$ , Acetone, rt., 90-94 %; c)  $\text{Mg}$ ,  $\text{I}_2$  (cat.),  $\text{B}(\text{OEt})_3$ ,  $\text{NH}_4\text{Cl}$  (sat'd), 80-85 %; d) *t*-BuLi,  $\text{B}(\text{OEt})_3$ ,  $\text{NH}_4\text{Cl}$  (sat'd), 77-80 %.

regioisomers. Isolation of bromogiuacol from the reaction mixture is achieved by Kugelroh distillation. The next step involved methylation of the phenol with methyl iodide in acetone, employing potassium carbonate as the base. These reactions typically gave a 90-94 % yield of the dimethyl bromocatechol. In the next step the 1,2-dimethoxybromobenzene (**272**) was converted into the corresponding boronic acid (**273**). The boronic acid was obtained by using either Grignard conditions or lithium halogen exchange with *t*-butyllithium. The Grignard conditions gave better overall yields.

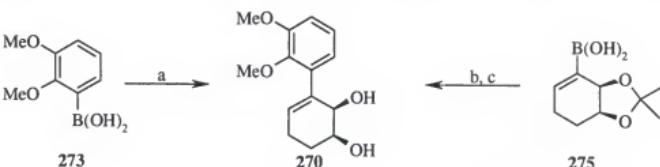
The other coupling partner became available from diimide reduction of the chiral cyclohexadiene diol **248**, with potassium azodicarboxylate (PAD). This procedure, which has been optimized in the Hudlicky group, typically gives about 90-95 % of the reduced product **247** (Scheme 52). We also synthesized the boronic acid derived from vinyl bromide **247** with the intent of coupling it with 1,2-dimethoxybromobenzene **272** (Scheme 52). Conversion of acetonide **274** to the boronic acid **275** proceeded with low

yields (45-50 %) hence making this route to the coupled product unfavorable.



**Scheme 52.** Conditions: a) PAD, HOAc, MeOH, 0° C-rt., 14 h, 90 %; b) DMP, Acetone, TsOH, 95%; t-BuLi, B(OEt)<sub>3</sub>, -78°C, NH<sub>4</sub>Cl (sat'd), 45-50 %.

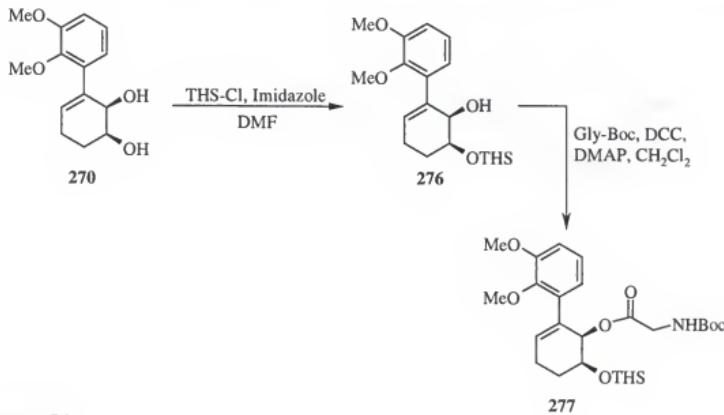
We now turned our attention to the Suzuki Coupling<sup>81,82</sup> step, a technique which has become one of the more efficient methods of bond formation between an aromatic ring and an sp<sup>2</sup> center. In our hands typical conditions involved the use of tetrakis triphenylphosphine palladium (Pd(PPh<sub>3</sub>)<sub>4</sub>) as the catalyst and a benzene/ ethanol solvent system with 2M Na<sub>2</sub>CO<sub>3</sub> as the base. The reactions were normally complete after three hours under reflux conditions. Yields were in the 75-80 % range and this was very crucial since the Suzuki coupling was one of the key steps in our synthesis (Scheme 53).



**Scheme 53.** Conditions: a) 0.03 % eq. Pd(PPh<sub>3</sub>)<sub>4</sub>, 2M Na<sub>2</sub>CO<sub>3</sub>, 247, PhH-EtOH, reflux; b) 0.03 % eq. Pd(PPh<sub>3</sub>)<sub>4</sub>, 2M Na<sub>2</sub>CO<sub>3</sub>, 274, PhH-EtOH, reflux; c) H<sup>+</sup>, THF.

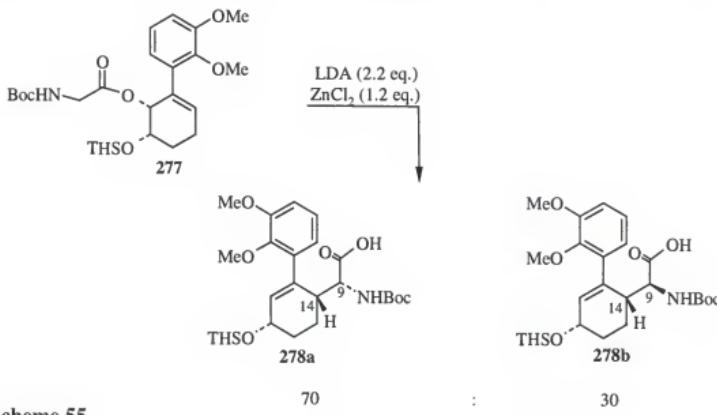
Claisen I-First attempt of Kazmaier Claisen on Morphine Precursor

To perform the Claisen rearrangement, we planned to take advantage of the remaining allylic alcohol unit in the bicyclic intermediate **270**. In order to ensure selective conversion of the proximal hydroxyl group into the glycinate ester we first had to protect the distal hydroxyl group as its silyl ether. The thexyldimethylsilyl (TDS) group was well suited for our substrate because its bulky nature ensures the protection of the least hindered hydroxyl group, which in this case is the distal hydroxyl. Yields for the step are typically around 90% for TDS-ether **276**. Less bulky silylating groups like TMS-Cl tend to lead to a large percentage of product resulting from lack of selectivity in the protection of the distal and the proximal hydroxyl groups. The reaction involves first, generating the imidazole-TDS complex at -12° C followed by addition of the diol (**270**) to the reaction mixture. Our efforts led to isolation of silyl ether **276** (Scheme 54). The next stage in the synthesis required the functionalization the proximal hydroxyl group as a glycinate ester,



Scheme 54

the Claisen rearrangement precursor. One of the standard procedures for achieving this type of transformation involves a DCC coupling.<sup>75</sup> In our hands the DCC coupling conditions worked well with Boc-glycine, DCC and catalytic DMAP. Yields ranged from 70–85%. Careful workup of the reaction mixture, which requires removal of the reaction solvent ( $\text{CH}_2\text{Cl}_2$ ) followed by precipitation of the dicyclohexylurea by-product with diethyl ether a procedure which usually removes about 80 – 85% of the dicyclohexyl urea (DCU) by-product. Column chromatography is then used to purify the crude mixture. With the glycinate ester **277** in hand we were ready to perform what would be the key step in our approach to morphine. A [3.3] sigmatropic rearrangement to establish the chiral centers at C9 and C14 (morphine numbering). As previously discussed, the Kazmaier-Claisen rearrangement provided the best opportunity to perform this transformation. The conditions involve the addition of Lewis acid (usually  $\text{ZnCl}_2$ ) to a

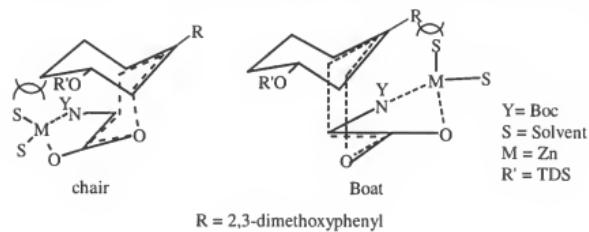


Scheme 55

solution of the glycinate ester in THF. After about 15 minutes of stirring the reaction mixture is cooled to -78° C and the base (usually LDA) is added. The reaction mixture

then allowed to warm slowly to room temperature over 36-48h. According to Kazmaier, the rearrangement usually occurs between -10° - 0° C. In our hands we observed very good conversion of starting material to products, with yields of rearranged acids averaging between 75 - 85% but there were two significant problems. 1) The ratio of the rearranged products **278a** and **278b** were opposite to that expected. We anticipated the product with a syn relationship between the proton at C14 and the nitrogen at C9 to be the major product. 2) The two rearranged acids possessed very similar spectroscopic properties so initially it was difficult to ascertain the identity of the isomers. 3) These compounds were virtually inseparable using standard chromatographic techniques even after their derivatization into the corresponding methyl esters.

The fixed enolate geometry that results from chelate formation in the Kazmaier-Claisen rearrangement causes the stereochemical outcome of the rearrangement to be a function of the transition state that the reaction proceeds through. For cyclohexyl substrates the unfavorable steric interactions in the chair transition state (Figure 3)



**Figure 6.** Chair vs boat transition states in the Kazmaier Claisen Rearrangement of morphinan intermediates.

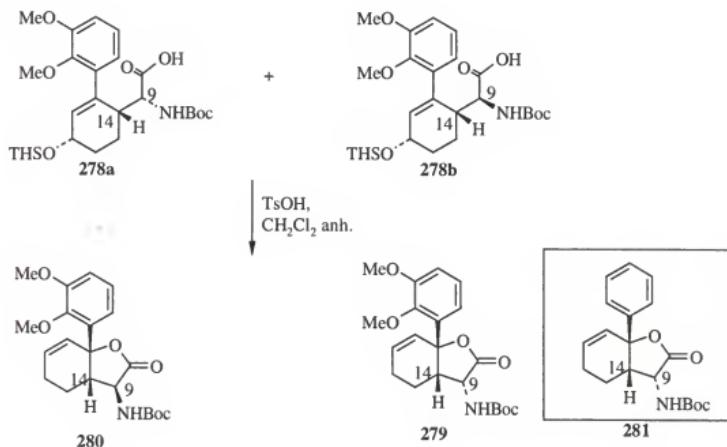
the cyclohexyl ring and the metal chelate, causes this transition state to be less preferred to the boat transition state, which is devoid of such interactions. It is very important to

note that Robert Ireland<sup>89,90</sup> who performed rearrangements on silyl ketene acetal analogues of these compounds, observed that both transition states could operate depending on the size and position of the substituents on the cyclohexyl ring. The effect of the large THS group can be neglected, but considerations of the dimethoxy phenyl substituent, which is in the  $\alpha$ -position to the allylic carbon, reveals that in the boat transition state this substituent might have an unfavorable steric interaction with the solvated metal (Figure 6). This leads to two steric arguments; 1) in the chair transition state there is an unfavorable interaction between the solvated metal and the cyclohexyl ring, 2) in the boat transition state the steric interactions are between the aromatic ring substituent and the solvated metal. As a result of these opposing steric interactions, the energy difference between the two transition states is very small, leading to product formation from both pathways. In our case the chair transition state is favored resulting in 70: 30 ratio of products.

As previously stated the rearranged acids **278a** and **278b** had similar spectroscopic properties, and they were virtually inseparable by standard chromatographic techniques. One of the options we explored to obtain pure samples of each was to derivatize these acids into the corresponding lactones, which would offer a more rigid structure with the anticipation that this might help in the identification of the acids. This transformation was achieved with tosic acid in anhydrous methylene chloride resulting in the formation of the corresponding lactones from the mixture of the epimeric acids (Scheme 56). Even though two possible lactones could have been obtained from this reaction we only observed the lactone derived from the trapping of the benzylic carbocation. Indeed in this way we were able to obtain dimethoxy phenyl lactone **279** in

pure form and were able to obtain spectral data for the compound. Lactone **280** was also

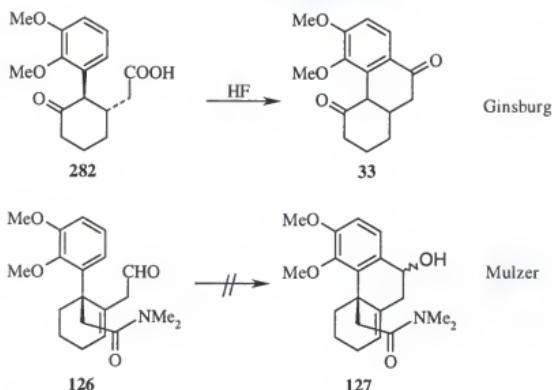
**Scheme 56**



isolated and easily converted to lactone **279** through an epimerization reaction with DBU. The data obtained was compared to phenyl lactone **281** which had been synthesized earlier and whose identity had been confirmed by X-ray crystallography.

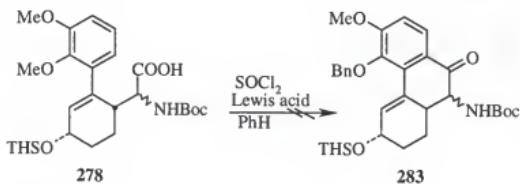
#### Friedel-Crafts Attempt at C10-C11 Closure

Even though we were unable to separate the two epimeric acids **279a** and **279b** we saw an opportunity to study the feasibility of the C10-C11 bond (morphine numbering) closure, through a Friedel-Crafts type reaction. We had conflicting literature precedence for this transformation. Ginsburg<sup>35</sup> was able to close the C10-C11 bond under acid conditions from the intermediate acid **282**. Although Ginsburg's intermediate contains the same bicyclic skeleton as in our example, his compound is much simpler and essentially has only one more functional group, the ketone at C5 (morphine numbering).



**Scheme 57**

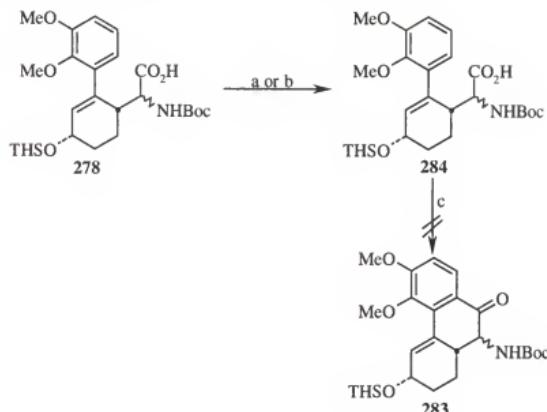
Using hydrofluoric acid he was able to achieve the Friedel-Craft annulation, to obtain the desired diketone **33**. Mulzer,<sup>21-25</sup> in his morphine synthesis, made intermediate **126** which also contained the bicyclic unit comprising the A and C-rings of morphine and essentially resembles that of Ginsburg, with the exception of the presence of the dimethylamido group resulting from a prior Eschenmoser-Claisen rearrangement step. Mulzer was not able to achieve annulation of the B-ring on the aldehyde upon treatment with various Lewis acids (Scheme 57). With these two contrasting results it was difficult to make any predictions as to the outcome of our attempts at B-ring closure. Starting from acid **278**, we derivatized it as the acid chloride using three different conditions.



**Scheme 58**

Initially we used thionyl chloride as the reagent for this transformation. We realized that these conditions (Scheme 58) were too harsh because we observed cleavage of the thexyl and Boc- protecting groups and or decomposition of the starting material even before addition of the Lewis acid. We saw no evidence of cyclized product (**283**) in the reaction mixtures and hence decided to resort to milder conditions for synthesizing the intermediate acid chloride. The conditions that we decided to work with involved either making the acid chloride by using oxalyl chloride/DMF or  $\text{PPh}_3/\text{CCl}_4$  using conditions analogous to that used by Rapoport<sup>91</sup> in his synthesis of tylophorine. Starting from acid **278**, we used a combination of oxalyl chloride and DMF to generate the acid chloride. Typically after four to six hours, we observed disappearance of the OH-stretch of the acid and appearance of a strong signal at 1780 corresponding to the acid chloride. At this point the Lewis acid was added and the reaction refluxed overnight. The various Lewis acids employed were  $\text{AlCl}_3$ ,  $\text{Me}_2\text{AlCl}$ ,  $\text{ZnCl}_2$  and  $\text{SnCl}_4$ . The reactions typically after workup led to recovery (Scheme 59) of starting material and a small percentage of by-product due to cleavage of the Boc-protecting group. The results from the triphenyl phosphine/carbon tetrachloride reaction were similar to the oxalyl chloride/ DMF reaction, here too no product from closure of the C10- C11 bond was isolated. Mulzer<sup>25</sup> in his discussion of his attempt at the Friedel-Craft reaction suggested that there might be a phenomenon similar to that of atropoisomerism of biphenyl compounds present in these types of substrates. This being the case our A-ring may be twisted out of conjugation with the cyclohexenyl ring making a Friedel-Craft type closure very difficult. The solution to this problem will be to either make the furan ring of morphine or to establish the nitrogen bridge first. This might help to hold the aromatic ring in a more preferable conformation that would allow

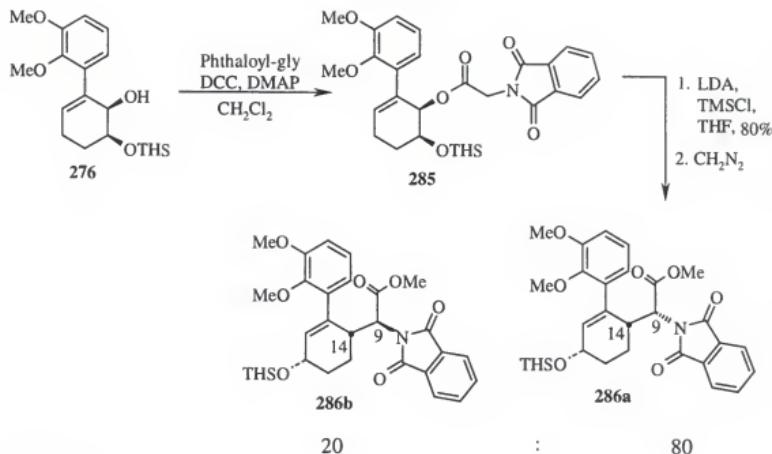
for a successful Friedel-Craft closure.



**Scheme 59.** Conditions: a) Oxalyl chloride, DMF, CH<sub>2</sub>Cl<sub>2</sub>; b) PPh<sub>3</sub>, CCl<sub>4</sub>, THF; c) Lewis acid (AlCl<sub>3</sub>, Me<sub>2</sub>AlCl, ZnCl<sub>2</sub> and SnCl<sub>4</sub>).

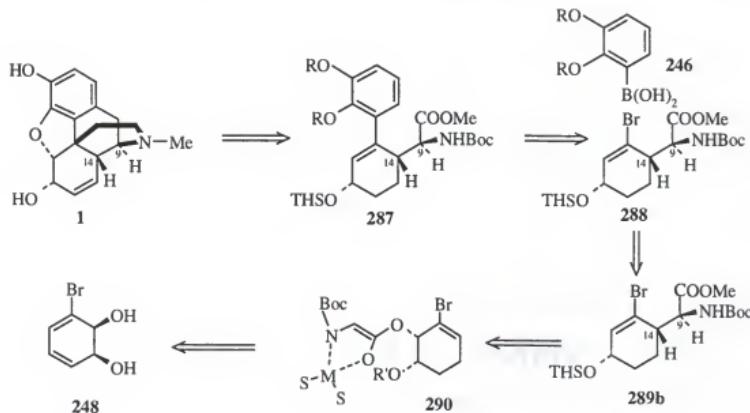
#### Claisen II-Ireland Claisen on Phthaloyl Ester

Our goal still remained to improve the selectivity of the Kazmaier Claisen rearrangement. One of the options we had not explored was a sigmatropic rearrangement under Ireland<sup>65,89,90</sup> conditions, which we hoped might lead to an improvement in the ratio of rearranged epimeric acids. To attempt the Ireland-Claisen rearrangement, we first functionalized the silyl ether **276** into the phthaloylester **285** (Scheme 60). Under Ireland conditions, we observed good conversion of starting ester to products but the product ratio again favored the undesirable epimer **286a**. More importantly, the epimers were also difficult to separate by column chromatography.



Scheme 60

At this point we reevaluated our synthetic approach to alleviate the stereoselectivity problem in the Kazmaier-Claisen rearrangement. We rationalized

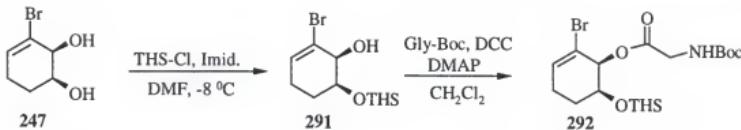


Scheme 61

that the source of the problem might be adverse steric interactions between the aromatic substituent and the metal chelate (Figure 6, pg 67). Our immediate solution to this problem was to attempt the Kazmaier-Claisen on the cyclohexenyl glycinate ester **290**, which has a bromine substituent in the  $\alpha$ -position to the allylic carbon. Such a substrate would possess a much minor steric interaction in the boat transition state between the solvated metal and the ring substituent (as discussed on pg 67) leading to a much improved product ratio. This also meant that the Suzuki Coupling step, which had previously preceded the Claisen rearrangement, would now be performed after the rearrangement. Our new general retrosynthetic scheme would be as represented by Scheme 61.

#### Claisen III-Kazmaier Claisen of Glycinate of Cyclohexadiene Diol

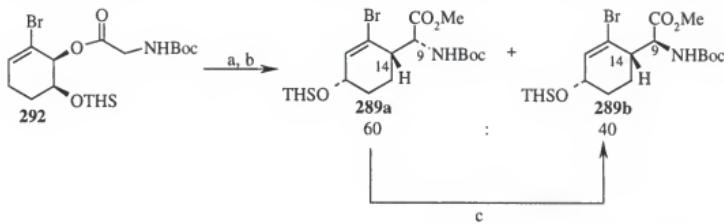
Starting from diol **247** we were able to protect the distal hydroxy group as the thexyldimethylsilyl ether **291**. Using DCC coupling protocol we obtained the glycinate ester **292**. We were now in a position to perform the Kazmaier Claisen on the precursor



Scheme 62

**292.** Using 2.2 equivalents of LDA and 1.4 equivalents of  $\text{ZnCl}_2$  we were able to obtain rearranged product epimeric at C9. We observed the yields for the transformation increase from 75% to 80-85%; the ratio of the rearranged acids epimeric at C9 also decreased slightly from a 70: 30 ratio to a 60: 40 ratio in our favor. But the best aspect of

this reaction was the fact that these epimeric acids, converted to their corresponding methyl esters could be separated by silica gel column chromatography. More importantly the faster-eluting major isomer **289a** could be equilibrated to the  $\beta$ -isomer (the desired epimer for our morphine synthesis) by an epimerization reaction with DBU. Starting from isomer **289a**, we are able to obtain a 1: 1 mixture of epimers after 96 hours in refluxing THF. Similar epimerization reactions with TFA and NaOMe gave a 4: 1 and 5: 1 ratio of epimers respectively. Even though the reaction is still non-stereoselective, we had found a way to obtain the epimer with the correct stereochemistry at C9 and C14. This was a huge breakthrough in our synthetic approach because it meant that we now had the opportunity to carry out an enantioselective synthesis of morphine.

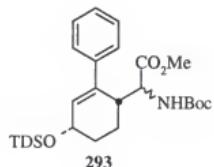


**Scheme 63.** Conditions: a) LDA (2.2 eq.), ZnCl<sub>2</sub> (1.4 eq.), THF, -78° C, 80%; b) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, 90%; c) DBU, THF, reflux, 65%.

We had also achieved control of the C9 and C14 (morphine numbering) stereocenters, which is very crucial to a successful morphine synthesis.

During this period of time we entered into a collaborative project with scientists at Procter and Gamble Pharmaceuticals who were interested in compounds to be used as scaffolds in their matrix metallo proteinase (MMP) inhibitors studies. Dr. Hudlicky recognized structural similarities between their targets (hydroxamic acids with an *R*-

configuration at the  $\alpha$ -center of the amino acid) and some of the compounds synthesized from the Kazmaier Claisen rearrangement during the morphine synthesis model study.



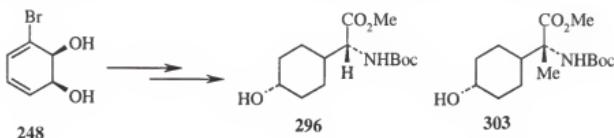
**Figure 7.** Structure of morphine precursor used in initial MMP screen.

To our surprise, ester **293** as a mixture of *R* and *S*-isomers at  $\alpha$ -center of the amino acid side chain showed MMP inhibition. This led to the initiation of the collaborative project with Proctor and Gamble Pharmaceuticals where the goal was to synthesize esters of the type **293** to be evaluated for biological activity as MMP inhibitors. This was a great opportunity because it gave us the occasion to apply our chemistry to industrial scale projects. The next section will describe some of the efforts made in the synthesis of matrix metallo proteinase inhibitors in a collaborative effort with researchers at Procter and Gamble Pharmaceuticals.

#### Synthesis of Matrix Metalloproteinase Inhibitors (MMP's)

Researchers at Procter and Gamble have been exploring the synthesis of unnatural amino acids to be used as scaffolds in the preparation of potent matrix metalloproteinase inhibitors (MMP's).<sup>92-95</sup> MMP inhibitors have shown activity as antagonists of various diseases where tissue remodeling plays a key role,<sup>96</sup> including osteoarthritis,<sup>97,98</sup> rheumatoid arthritis,<sup>99</sup> tumor metastasis,<sup>100</sup> multiple sclerosis<sup>101</sup> and congestive heart failure.<sup>102</sup> The structural features of their target, resembled ester **289a** which interestingly

was the undesired isomer from the Kazmaier Claisen rearrangement (Scheme 63).

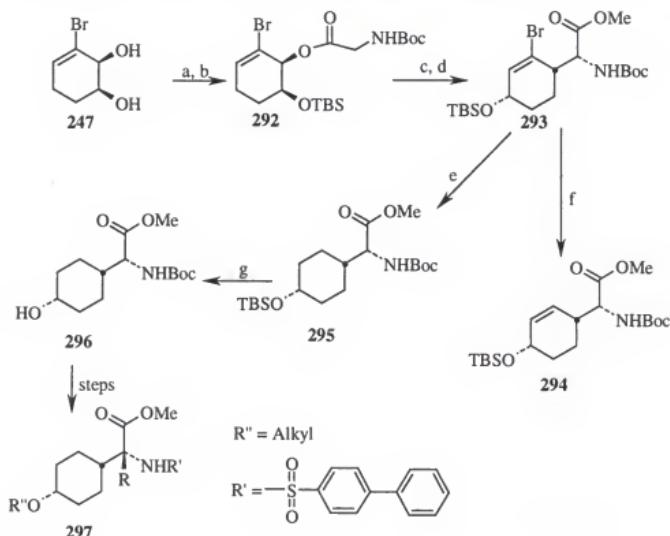


**Scheme 64**

We prepared a series of cyclohexylglycine and cyclohexylalanine derivatives of the type **296** and **303** (Scheme 64) to be utilized as intermediates for the synthesis of MMP inhibitors. Also as part of the collaborative project, the absolute stereochemistry of ester **289a** was determined unambiguously by X-ray crystallography (Figure 7). Esters **296** and **303** were synthesized using similar protocol as has been described earlier in the chapter. Approaches to compounds of this type through enolate alkylation or aldol type condensations are quite difficult, hence the Kazmaier Claisen provides a direct route to these unnatural amino acids with control of stereoselectivity and respectable yields.

Starting from the diol **247**, a two step sequence involving protection of the distal hydroxyl group as the TBS-ether, followed by esterification of the proximal hydroxyl group by DCC coupling rendered glycinate ester **292** (Scheme 65). We achieved the rearrangement to the corresponding acids via Kazmaier Claisen conditions. Diazomethane was then utilized in the conversion of the acids to the methyl ester derivatives. The next step involved reduction of the vinyl bromide with Adam's catalyst at 40 psi with triethylamine as the proton scavenger. Finally tetrabutyl ammonium fluoride mediated deprotection of the TBS group rendered the alcohol **296** which

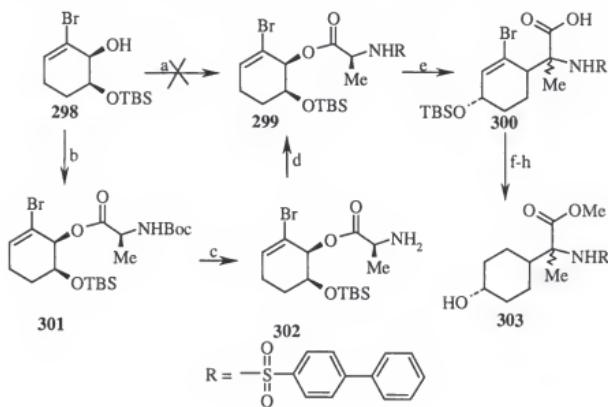
underwent other proprietary transformations before being used in MMP testing. Because



**Scheme 65.** Conditions: a) TBS-Cl, imidazole, DMF, -12 °C, 85%; b) DCC, DMAP, *N*-Boc-glycine or *N*-Boc-alanine, CH<sub>2</sub>Cl<sub>2</sub>, 80%; c) ZnCl<sub>2</sub>, LDA, THF, -78 °C, 75%; d) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, 90%; e) H<sub>2</sub>/PtO<sub>2</sub> (40 psi), Et<sub>3</sub>N, MeOH, 75%; f) *n*Bu<sub>3</sub>SnH, AIBN, PhH.g) TBAF, THF, 80%.

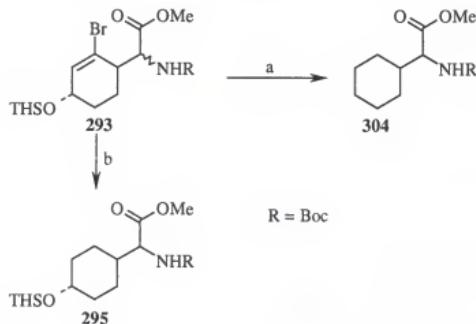
of the success of the Claisen with the glycine ester, we planned to prepare sulfonamide **299** through a DCC coupling reaction with TBS-ether **298** and the alanine moiety already functionalized as the sulfonamide. This reaction proved unsuccessful, hence we prepared ester **301** and following the removal of the Boc protection group, were able to install the sulfonamide to obtain **299**. The Kazmaier Claisen rearrangement of **299** to **300** worked smoothly as in the case of the glycine ester (Scheme 66) even though yields were lower probably due to the lower chelating potential of the sulfonamide as compared to the carbamate in structure **292**. The synthesis of **300** also did not proceed with the same

diastereoselectivity as in the earlier cases presumably because of the increased size of the sulfonamide functionality leading to a decrease in preference for the chair transition



**Scheme 66.** Conditions: a) alanine N-sulfonamide, DCC; b) N-Boc alanine, DCC; c) TFA,  $\text{CH}_2\text{Cl}_2$ ; d) 4-methoxy-1,1'-biphenylsulfonyl chloride,  $\text{Et}_3\text{N}$ , THF; e)  $\text{ZnCl}_2$ , LDA, THF,  $-78^\circ \text{C}$ ; f)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ ; g)  $\text{H}_2$  (40 psi),  $\text{PtO}_2$ ,  $\text{Et}_3\text{N}$ ,  $\text{MeOH}$ ; h) TBAF, THF.

state. Even so, acids **300** were converted over three steps to methyl esters **303**, the precursors for MMP inhibitors. One of the more difficult steps in this project was the last

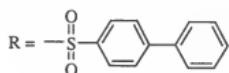


**Scheme 66.** Conditions: a)  $\text{H}_2$  (40 psi), 5% or 10% Pd-C,  $\text{MeOH}$ ; b)  $\text{H}_2$  (40 psi),  $\text{PtO}_2$ ,  $\text{Et}_3\text{N}$ ,  $\text{MeOH}$ .

step involving the removal of the vinyl bromide through hydrogenation. Initial attempts at this transformation utilized 10% and 5% Palladium on Carbon (Pd/C) at 40 psi in methanol. Even though this resulted in the removal of the vinyl bromide it also resulted in hydrogenolysis of the silyl ether leading to the isolation of ester **304**. Even though ester **304** was devoid of the hydroxyl group, the hydroxamic acid derivative this compound surprisingly showed some activity as an MMP inhibitor. After investigating several other conditions we discovered that using Adam's catalyst ( $\text{PtO}_2$ ) in methanol at 40 psi with

**Table 7.** MMP inhibition activity for glycine and alanine analogs.

	$\text{IC}_{50}$ (nM) <sup>a</sup>			
	305	306	307	308
MMP-2	12	20	38	251
MMP-3	1,220	2,490	3,795	6,150
MMP-13	30	176	131	338



triethylamine as a proton sponge works nicely leading to isolation of the silyl ether **295** in 89% yield.

With the completion of the collaborative project, we turned our attention back to morphine synthesis; we now had a stereospecific way of obtaining the methyl ester **289b**

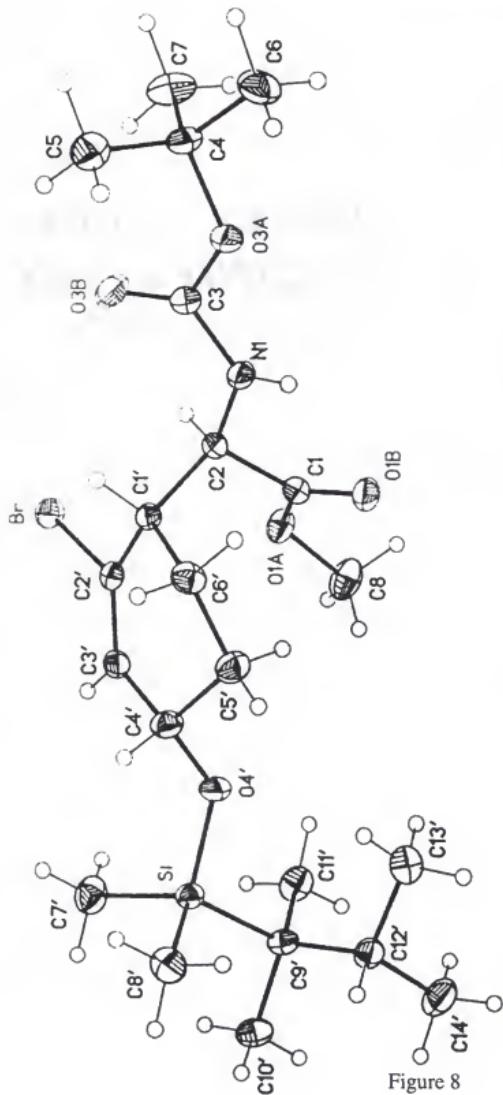
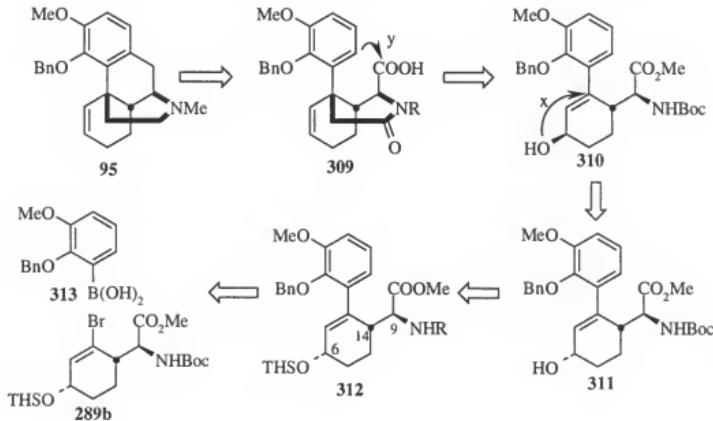


Figure 8

(Scheme 60). The next step involved the coupling of the methyl ester with an aromatic boronic acid to obtain our crucial bicyclic intermediate **242** using the Suzuki conditions that by now had been optimized for the morphine project (Scheme 49, pg 57).

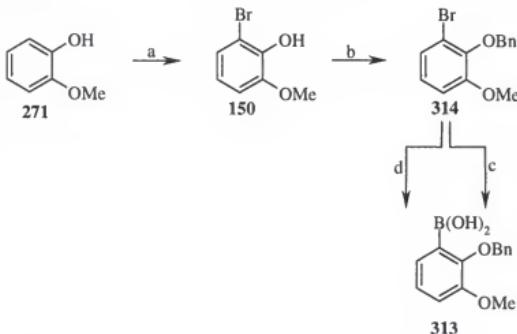
#### Second Generation Synthesis- Overman's Intermediate via Claisen Rearrangement

In this section the efforts towards synthesizing the Overman<sup>53</sup> intermediate **95** (pg 21-22, Chapter 1) are described. The target was chosen for two main reasons, first the synthesis of the Overman intermediate would allow us to achieve a formal total synthesis of morphine since dihydrocodeinone (**88**) was synthesized in three steps from the Overman intermediate. Also, after coupling ester **289b** with an appropriate aromatic piece this bicycle would possess all the functionality needed to achieve the synthesis of the Overman intermediate. Retrosynthetically our goal was to arrive at the Overman intermediate through a Friedel-Craft<sup>102,103</sup> reaction on acid **309**. Even though our earlier



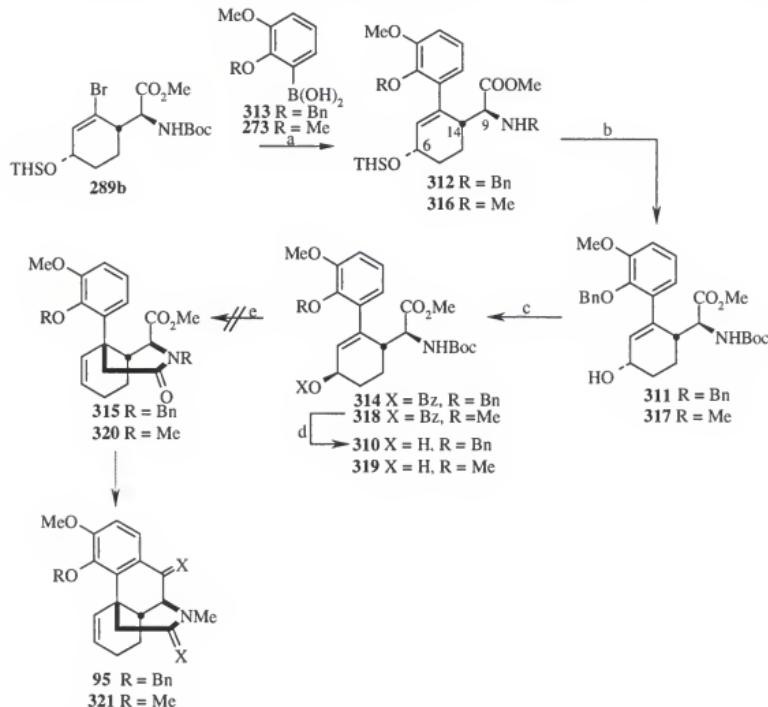
Scheme 68

attempts at the Friedel-Craft reaction were unsuccessful we were hopeful that with the construction of the nitrogen bridge, this precursor would have a more rigid structure with the aromatic ring in a favorable position to effect cyclization (path y, Scheme 68). The key step in this synthesis would be the setting of the C13 quaternary center by a [3,3]-sigmatropic rearrangement. The options available were an Ortho-ester Claisen<sup>104,105</sup> rearrangement or an Eschenmoser<sup>106,107</sup> type Claisen rearrangement using the allylic alcohol moiety in precursor **310** (path x, Scheme 68). Alcohol **310** could in turn be synthesized through a Mitsunobu<sup>108</sup> reaction of alcohol **311**. Compound **311** could be achieved from a two-step sequence involving a Suzuki reaction to couple the methyl ester and the aromatic boronic acid followed by a fluoride deprotection of the silyl ether. Boronic acid **313** was synthesized (Scheme 69) using the same protocol that was used for the synthesis of the dimethoxy boronic acid **273** (pg 61) with similar results in terms of yield. With boronic acid **313** in hand we were able to achieve coupling with ester



**Scheme 69.** Conditions: a)  $\text{Br}_2$ , tert-butylamine, toluene,  $-78^\circ \text{ C}$ , 60-62 %; b)  $\text{BnBr}$ ,  $\text{K}_2\text{CO}_3$ , Acetone, rt., 90-94 %; c)  $\text{Mg}$ ,  $\text{I}_2$  (cat.),  $\text{B}(\text{OEt})_3$ ,  $\text{NH}_4\text{Cl}$  (sat'd), 82-86 %; d) t-BuLi,  $\text{B}(\text{OEt})_3$ ,  $\text{NH}_4\text{Cl}$  (sat'd), 75-80 %.

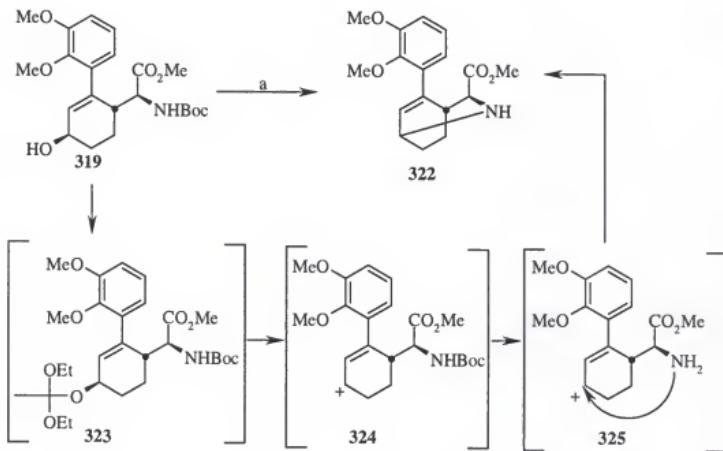
**289b** to obtain the bicyclic **312**. The following reactions were performed on the 2,3-dimethoxyphenyl and 2-benzyloxy-3-methoxyphenyl analogs as shown in Scheme 70 but the description of the process will focus on the benzyl-protected analog. To ensure the correct regio-chemistry of the Claisen rearrangement we proceeded to invert the alcohol at C6 (morphine numbering). This process began with a tetrabutyl ammonium fluoride



**Scheme 70.** Conditions: a) 0.03 % eq. Pd(PPh<sub>3</sub>)<sub>4</sub>, 2M Na<sub>2</sub>CO<sub>3</sub>, **313**, PhH-EtOH, reflux; b) TBAF, THF; c) DEAD, PBu<sub>3</sub>, BzOH, THF, -10 °C – rt; d) K<sub>2</sub>CO<sub>3</sub>, MeOH.

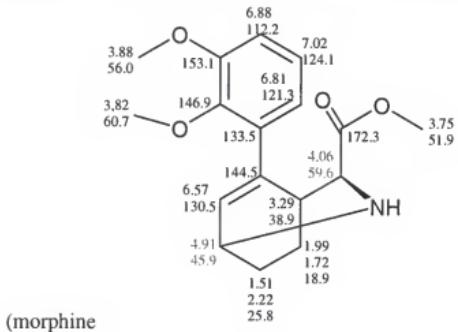
(TBAF) deprotection of the thexyldimethylsilyl group to give alcohol **311**. The free  $\alpha$ -faced alcohol was then inverted with a Mitsunobu<sup>108,109</sup> reaction (Scheme 70) using

tributylphosphine, benzoic acid and DEAD (diethylazodicarboxylate). The benzoate thus formed was hydrolysed easily with  $K_2CO_3$ / MeOH to obtain the inverted free alcohol **310**. With alcohol **310** in hand the next step was to attempt the Orthoester Claisen rearrangement. Typical conditions involve *in-situ* formation of the orthoester followed by subsequent acid catalyzed rearrangement at temperatures ranging from 160 °C to 180 °C. Using a combination of triethyl orthoacetate and catalytic amounts of propionic acid we attempted the Orthoester Claisen using three different solvent systems (Scheme 71). The reactions were run either in neat triethyl orthoacetate, xylenes or in toluene. The results obtained were quite consistent in all three solvents. The product of the attempted orthoester-Claisen rearrangement was a compound resulting from cleavage of the ortho ester intermediate and subsequent trapping of the resultant allylic cation by our amine



**Scheme 71.** Conditions: a) i) triethylorthoacetate, propionic acid (cat.) 160°C-180°C; ii) triethylorthoacetate, propionic acid (cat.), xylenes, 160°C-180°C; iii) triethylorthoacetate, propionic acid (cat.), toluene, 160°C-180°C.

functionality. We suspect that thermal and/or acid catalyzed decomposition of the carbamate protecting group leads to the free amine, which then traps the allylic cation. In the first generation synthesis (pg 68) we used the cleavage of the C-O bond (at C6 morphine numbering) to our advantage in determining the identity of our rearranged acids through a lactonization reaction. Unfortunately in this case it was a significant problem because cleavage of the ortho ester always occurred before any potential rearrangement and so we were unable to proceed further with this route towards Overman's intermediate. The identity of the orthoester-Claisen product was obtained using NMR experiments namely GHMQC and HETCOR. The sequence 5-6-7-8-14-9

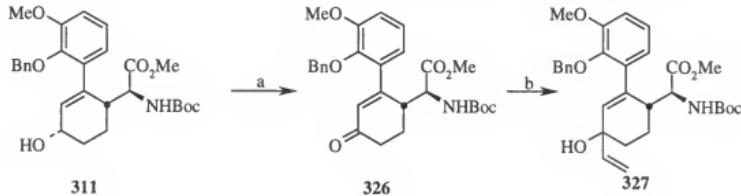


**Figure 9.** Assignment of Orthoester Claisen product.

numbering) was seen by the DQCOSY spectrum (H1- H1 correlation) as CH-CH-CH<sub>2</sub>-CH<sub>2</sub>-CH-CH-. The aryl group was confirmed to be in position 13 by the long range couplings H(11)-C(13) and H(5)-C(12) as seen in the GHMBC spectrum. The methyl ester was confirmed to be in position 9 by the cross-peak H(9)-C(CO). With these correlational experiments the molecule was assembled with the exception of the two open valencies at C6 and C9. The carbon chemical shifts of the atoms suggest that they are

bonded to the nitrogen atom. This molecular formula was further confirmed by HRMS. From these correlation experiments the proton and carbon signals were correctly assigned as shown in Figure 9. From long range coupling experiments, the connectivity of our molecule was confirmed when we observed a long range coupling between the proton at C6 (morphine numbering) whose signal appears at 4.91 ppm and the proton on the  $\alpha$ -center of the amino acid (C9 morphine numbering) whose signal appears at 4.06 ppm. This was further confirmed by a long-range  $^1\text{H}$ - $^{13}\text{C}$  coupling between the proton signal at 4.91 ppm and the carbon signal at 59.6 ppm, which belongs to the carbon at the  $\alpha$ -center (C9 morphine numbering).

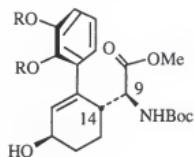
Since we now had alcohol **311** in our possession, we reasoned that we could still establish the C13 quaternary center by employing a conjugate addition of an



**Scheme 72.** Conditions: a) PCC,  $\text{CH}_2\text{Cl}_2$ ; b)  $(\text{H}_2\text{C}=\text{CH})_2\text{CuMgCl}$ , THF,  $-78^\circ\text{C}$ .

organocuprate with the enone obtained from oxidation of the alcohol. Alcohol **311** was subjected to PCC oxidation conditions to obtain enone **326**. Upon addition of a vinyl cuprate, no 1,4 addition product was isolated. The major product of the reaction was the

1,2-addition adduct **327**. It is our suspicion that because this bicyclic compound

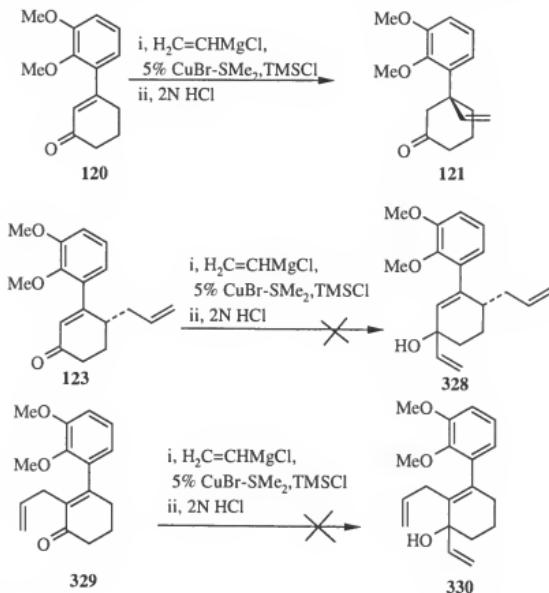


**Figure 10.** Possible atropoisomerism of morphinan intermediates

exhibits atropoisomerism, the aromatic ring is twisted out of conjugation with the cyclohexenyl ring (Figure 10). This probably causes the aromatic ring to be perpendicular to the cyclohexyl ring so any substituent in the 2-position of the aromatic ring (benzyl in this case) sterically hinders any attack to the C13 center.

In summary our attempt at the Overman intermediate failed because of two main problems. The first problem, which was encountered in the orthoester-Claisen, is a trend that we had observed earlier in the synthesis (Scheme 56, pg 68) and used to our advantage. The C6 (morphine numbering) position easily ionizes if any good leaving groups are present because of the stability of the resultant allylic carbocation which is resonance stabilized by the aromatic ring. Under catalytic or stoichiometric acid conditions, the orthoester intermediates are cleaved either through an S<sub>N</sub>1 or an S<sub>N</sub>2 mechanism to yield products of the type **322**. The second problem is of a steric nature, cuprate addition to the C13 (morphine numbering) center led to recovery of 1,2-addition products exclusively. Mulzer<sup>25</sup> in his synthesis of morphine encountered the same problem in his attempt at conjugate addition to a similar substrate (Scheme 73). Initial model studies were successful at establishing what would be the C13 center by cuprate addition. When the same reaction was applied to more advanced intermediates **123** and

329 the conjugate addition yielded only 1,2-adducts.  $^1\text{H-NMR}$  spectra of Mulzer's intermediates demonstrated the presence of atropoisomers and this led to his assumption that these intermediates exhibited atropoisomerism. In our case high temperature  $^1\text{H-NMR}$  experiments were inconclusive because even though we observed the presence of two isomers it was impossible to determine whether the isomerism was from the carbamate moiety or due to atropoisomerism. The result of the atropoisomerism is that



**Scheme 73**

the aromatic residue becomes more or less perpendicular to the double bond hindering any attack on the benzylic  $\text{sp}^2$ -hybridized carbon.

Alternative methods to Setting the C13 quaternary center.

At this point we had to assess the route to establishing the C13 quaternary center. We still had a couple of options available to achieve this task. The first option was to take advantage of some of the inherent properties in intermediate **311** to establish the C13 center. If indeed our assumption was correct and alcohol **311** (Scheme 70) was prone to exhibit atropoisomerism, then a tether at the 2-position of the aromatic ring becomes a very important group. The effect of the atropoisomerism would essentially position the tether at the 2-position of the aromatic ring in a desirable position to effect either radical or nucleophilic attack of the C13 carbon. If the attack at C13 comes from the  $\beta$ -face of the molecule, this synthesis would eventually lead to morphine. An attack

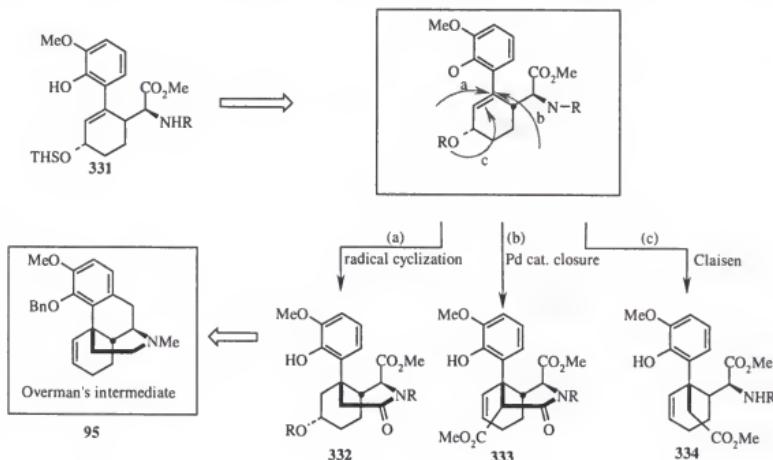
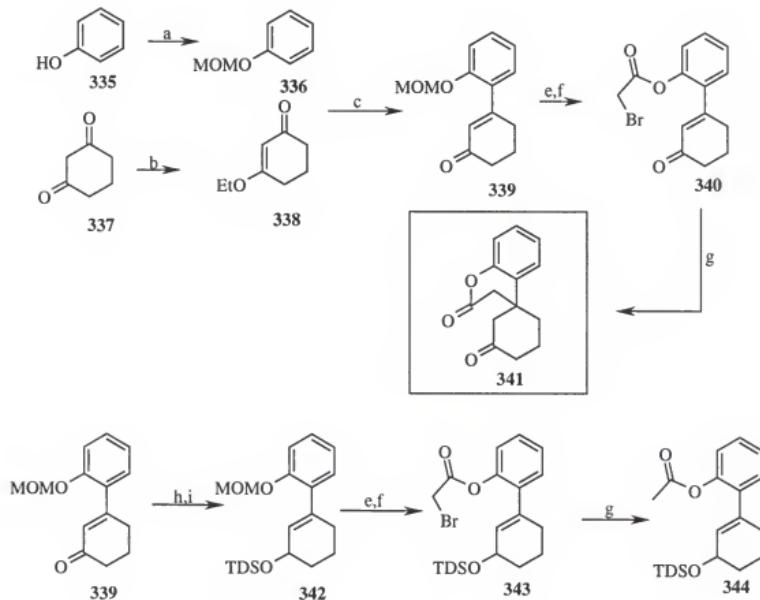


Figure 10. Strategy for establishment of C13 quaternary center.

from the  $\alpha$ -face would lead to *ent*-morphine. The second option would be to attempt the C13 attack from the amino ester side chain either through a palladium catalyzed SN<sub>2</sub>' reaction or a radical type attack.

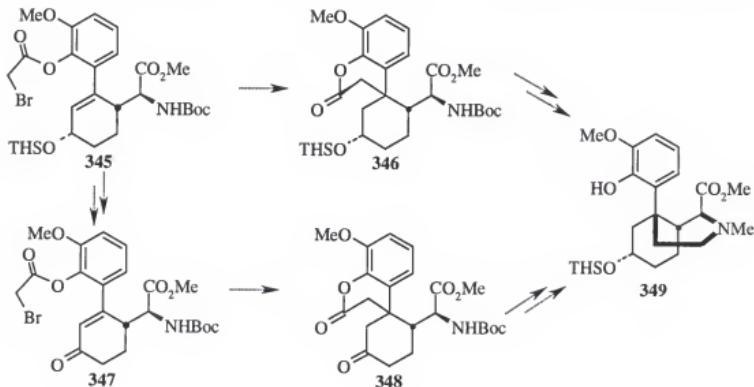
Before applying the alternate routes to the establishment of the C13 center to the morphinan intermediates we decided that a quick model study to ascertain the feasibility of these reactions would be in order. We prepared enone **340** and silyl ether **343** as shown in Scheme 74 from phenol and 1,3-cyclohexadione (**337**). Cleavage of the MOM



**Scheme 74.** Conditions: a) MOM-Cl, NaH, THF; b) EtOH, *p*TsOH, PhH; c) t-BuLi, THF; e) H<sup>+</sup>/THF; f) Bromoacetyl bromide, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; g) *n*Bu<sub>3</sub>SnH, AIBN, PhH; h) NaBH<sub>4</sub>, MeOH; i) TDS-Cl, imidazole, DMF.

protecting group from the bicyclic **339** afforded the intermediate alcohol, which was converted to the bromoacetate **340** the radical cyclization precursor. Silyl ether **343** was obtained from intermediate **342** after cleavage of the MOM-protecting group and subsequent appendage of the bromoacetate. The two bromoacetates were then subjected to radical conditions using a protocol previously used by Ogasawara<sup>60</sup> and coworker in their synthesis of 3,4-dimethoxy-7-morphinanone (pg 39, Ch. 1). The radical reaction failed to produce any cyclized product in the case of silyl ether **343**. Instead we observed the formation of the reduced product exclusively. This was not unexpected due to the fact that for that cyclization to work the reaction had to proceed from a stabilized ester radical to an unstable radical. On the other hand enone **340** subjected to the same conditions yielded the cyclized product **341** in 66% yield with recovery of about 15% of reduced product. With the success of the model study our attention focused on its application to the morphine synthesis.

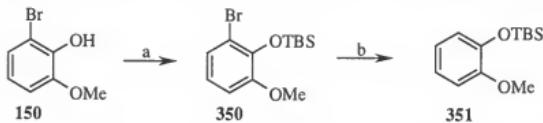
Our goal was to achieve the synthesis of intermediates of the type **345** or **347**



Scheme 75

(Scheme 75) in order to apply our model study to real morphinan intermediates. A successful radical closure would lead to the establishment of the C13 quaternary center; this would be followed by a translactamization reaction after deprotection of the Boc-group to establish the nitrogen bridge as shown in Scheme 75.

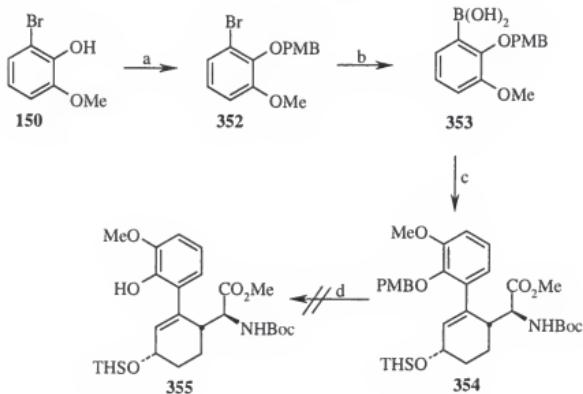
The first order of business was to redesign our aromatic ring with a protecting group in the 2-position that could be cleaved readily to allow for the appendage of the bromoacetyl group. The first protecting group we worked with was the TBS-group. Bromoguaiaicol **150** was readily converted to the TBS ether using triethylamine, DMAP and TBS-Cl. Unfortunately in the next step that involved the lithium halogen exchange and alkylation using triisopropyl borate, we realized that the TBS-group was too bulky



**Scheme 76.** Conditions: a) TBS-Cl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; b) B(OiPr)<sub>3</sub>, H<sup>+</sup>

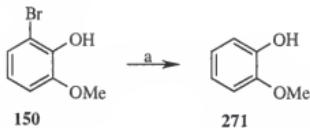
hence preventing the subsequent alkylation step. The only material isolated from the reaction was starting material and the reduced product **351** (Scheme 76). We were able to confirm the formation of the anion using deuterium exchange experiments. So we realized that the problem lay in the alkylation step. The next protecting group considered was the paramethoxybenzyl group (PMB). This was in theory an ideal protecting group for our synthesis because we had prior experience (in our approach to the Overman intermediate, Scheme 69, pg 83) on the synthesis of the benzyl protected boronic acid and reasoned that the synthesis of the PMB boronic acid would be analogous. Most importantly this group could be cleaved with DDQ, which in our estimation would not

affect any of our chiral centers or other protecting groups. Using  $K_2CO_3$  and acetone we protected bromoguaiacol as the PMB ether. In the subsequent step we successfully synthesized the boronic acid **353** using *n*-BuLi and triisopropyl borate.



**Scheme 77.** Conditions: a) PMB-Br,  $K_2CO_3$ , Acetone; b) *n*-BuLi,  $B(oipr)_3$ ,  $H^+$ ; c) 0.03 % eq.  $Pd(PPh_3)_4$ , 2M  $Na_2CO_3$ , **289b**, PhH-EtOH, reflux; d) DDQ,  $H_2O$ ,  $CH_2Cl_2$ .

The Suzuki coupling of the boronic acid with methyl ester **289b** (Scheme 77) worked quite well to afford PMB ether **346**. At this point we attempted cleavage of the PMB group in order to append the bromoacetyl group on the phenol. Unfortunately this step led mostly to decomposition of our starting material. With the failure of the PMB route

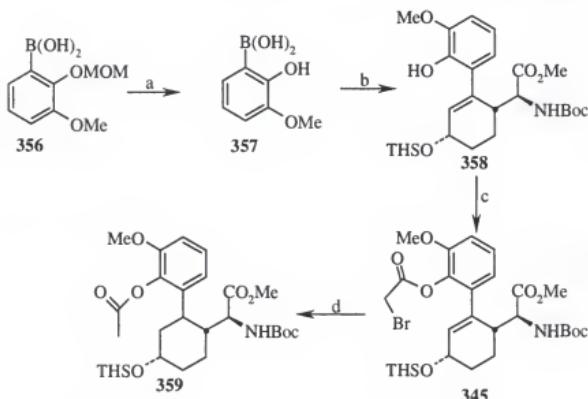


**Scheme 78.** Conditions: a) *n*-BuLi,  $B(oipr)_3$ ,  $H^+$ ;

we wondered if we could synthesize the boronic acid directly from bromoguaiacol. This would give us a free phenol going into the coupling step and negate the need for a protecting group. This reaction (Scheme 78) was not successful and resulted in isolation of guaiacol **271** exclusively.

The MOM-protecting group was considered because of the ease of removal of the group. Protection of bromoguaiacol as the MOM-phenol proceeded smoothly as did the step to make the boronic acid. Throughout this study of protecting groups we had speculated about the possibility of performing the Suzuki coupling on the free phenol. The Suzuki conditions require the use of 2M Na<sub>2</sub>CO<sub>3</sub> and the concern was whether the alkoxide of the phenol would couple as effectively as the protected phenol.

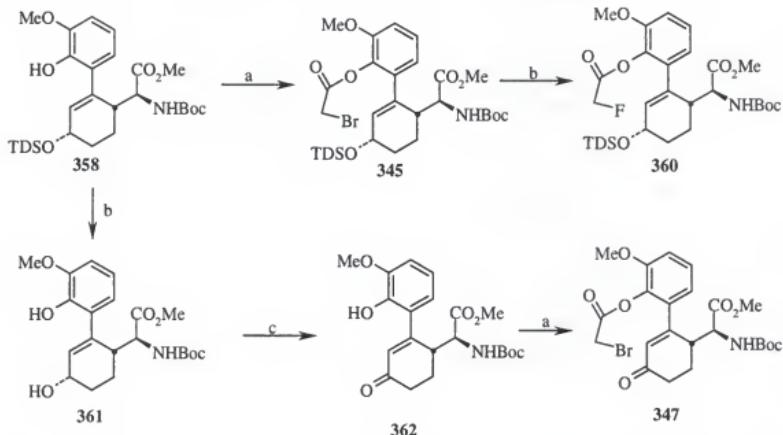
Starting from the MOM-protected boronic acid **356**, we were able to obtain the



**Scheme 79.** Conditions: a) TFA, CH<sub>2</sub>Cl<sub>2</sub>; b) 0.03 % eq. Pd(PPh<sub>3</sub>)<sub>4</sub>, 2M Na<sub>2</sub>CO<sub>3</sub>, **289a**, PhH-EtOH, reflux; c) Bromoacetyl bromide, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; d) *n*Bu<sub>3</sub>SnH, AIBN, PhH.

free phenol **357** with TFA in methylene chloride. The phenol was then coupled with methyl ester **289b** under Suzuki conditions (Scheme 79) leading to isolation of bicyclic

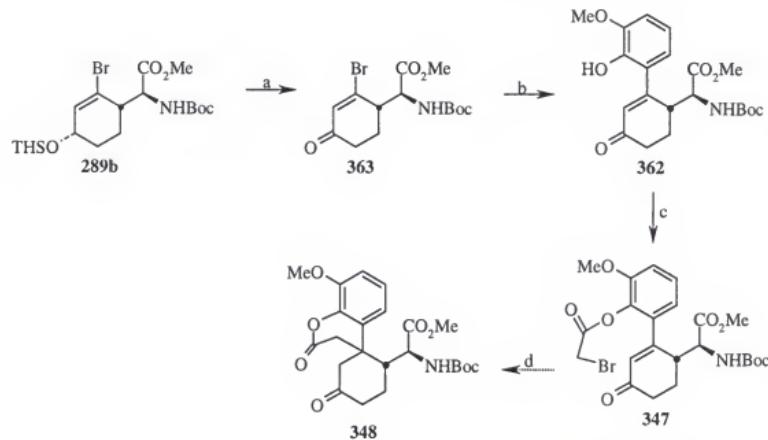
**358** albeit in a 45% yield. With the phenol in hand we were able to synthesize the bromoacetate derivative using DMAP and bromoacetyl bromide in methylene chloride. The radical reaction of bromoacetate **345** using the same conditions as was used in the model study resulted in the formation of the reduced product **359**. The synthesis of enone **347** proved to be more challenging than expected. Starting from phenol **358** we had two options available. We could first alkylate the phenol as the bromoacetate and then remove the silyl-protecting group followed by subsequent oxidation of the C6 (morphine



**Scheme 80.** Conditions: a) Bromoacetyl bromide, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; b) TBAF, THF; c) PCC or MnO<sub>2</sub> or Dess-Martin.

numbering) alcohol. Equally we had the option of initial removal of the silyl-protecting group followed by oxidation to the enone and then final alkylation of the phenol to form the bromoacetate. Preliminary evidence indicates the formation of a Finkelstein<sup>111</sup> type product in our attempt to cleave the silyl-protecting group in intermediate **345** in the presence of the bromoacetate as shown in scheme 80. Conversely we had problems with

the oxidation of allylic alcohol **361** probably due to reaction of the oxidant with the phenol. The yields for the oxidation step were very low (10- 15%) and so this route could not be used to obtain decent quantities of the enone **362**. Our final option was to first form the enone from the vinyl bromide and then achieve coupling with boronic acid **357**. Indeed this worked quite well with the isolation of the enone **362**. In the next step the phenol was converted to the bromoacetate, which was then subjected to the radical cyclization conditions. We are currently in the process of optimizing this reaction.

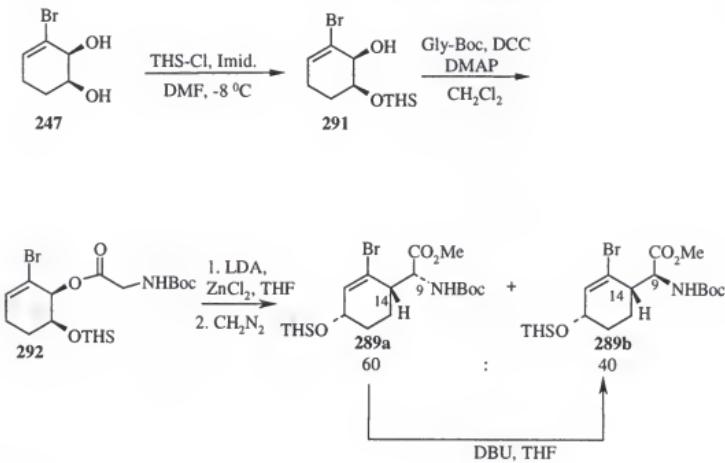


**Scheme 81.** Conditions: a) TBAF, THF; b) PCC,  $\text{CH}_2\text{Cl}_2$ ; c) 0.03 % eq.  $\text{Pd}(\text{PPh}_3)_4$ , 2M  $\text{Na}_2\text{CO}_3$ , **289a**, PhH-EtOH, reflux; d) Bromoacetyl bromide, DMAP,  $\text{CH}_2\text{Cl}_2$ ; e)  $n\text{Bu}_3\text{SnH}$ , AIBN, PhH;

## CHAPTER 4 CONCLUSION

### Summary and Conclusions

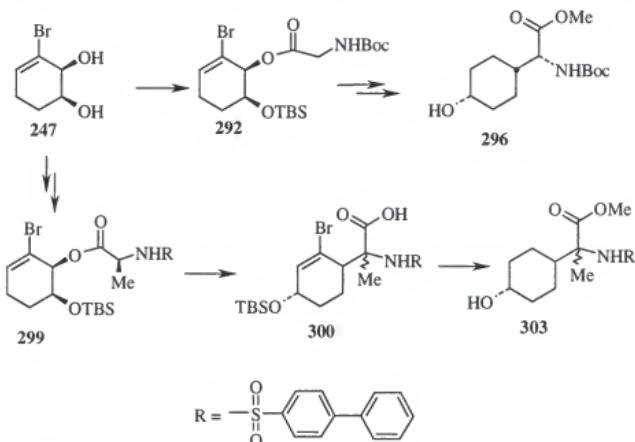
In the course of this project we have been able to successfully apply a chemoenzymatic approach towards morphinan alkaloids utilizing the Kazmaier Claisen rearrangement and the Suzuki Coupling reaction to obtain advanced intermediates towards morphine. Control of the C9 and C14 (morphine numbering) centers was



**Scheme 82**

achieved using a combination of Kazmaier Claisen rearrangement and epimerization reactions (Scheme 82). We were also successful in applying this chemistry to the synthesis of matrix metallo proteinase inhibitors (MMPs) in a collaborative project with

Procter and Gamble Pharmaceuticals (Scheme 83). Our most challenging endeavor has



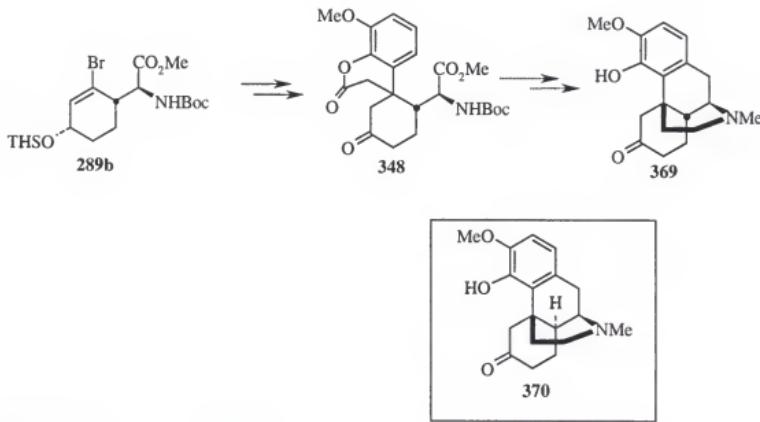
Scheme 83

been the attempts at establishing the C13 quaternary center. In our approach to the Overman intermediate we discovered the hindered nature of the C13 carbon and also the reasons for our unsuccessful Orthoester Claisen rearrangement. The problem can be summarized as lability of groups at the C6 (morphine numbering) position and steric hindrance at the C13 position due to what we suspect is atropoisomerism. We realized that we had an opportunity to achieve functionalization of the C13 center from either a tether on the 2-position of the aromatic ring or from the nitrogen side chain. Model studies confirmed the feasibility of a radical closure from a tether on the aromatic ring and the last part of the project has been dedicated to the synthesis of intermediates that would allow for the establishment of the C13 center through this reaction.

There are still a few options available to achieve functionalization of the C13 center. We have yet to attempt either a palladium catalyzed  $\text{SN}^2'$  closure or a

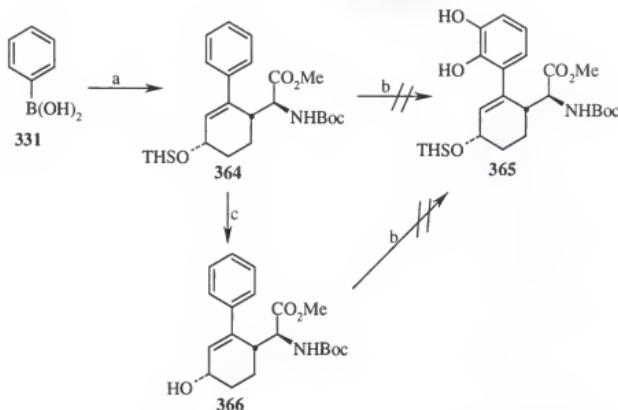
Reformatsky type reaction to establish C13. The morphinan intermediates allow for these reactions to be attempted either from the nitrogen side chain or from a tether on the phenol.

Establishment of the C13 center would be followed by a translactamization reaction to afford the nitrogen bridged intermediate of the type **369**. After a Friedel-Kraft reaction this intermediate begins to look very similar (Scheme 86) to one of the Gates' intermediates **370** from which morphine was synthesized in an additional 7 steps.



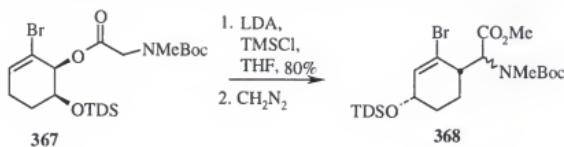
**Scheme 84**

In the course of the project we have also looked at ways to make this approach to morphine, practical. To this effect, we attempted the direct oxidation of intermediate **364** using a catechol dehydrogenase enzyme, which was recently discovered in the Hudlicky research group.<sup>112</sup> Success of such a transformation would eliminate 4 synthetic steps



**Scheme 85.** Conditions: a) 0.03 % eq.  $\text{Pd}(\text{PPh}_3)_4$ , 2M  $\text{Na}_2\text{CO}_3$ , **289b**, PhH, reflux; b) *E coli* pDTG 602, c) TBAF, THF;

from our synthesis. Unfortunately we ran into feasibility problems because the substrate **364** could not be dissolved in the aqueous media containing the bacteria even after cleavage of the THS-group to give the alcohol **366**. Even though this attempt was unsuccessful our goal still remains; to arriving at a truly chemoenzymatic synthesis of morphine (Scheme 85). It is still possible to arrive at compounds like **365** through an initial biooxidation of the aromatic piece followed by Suzuki coupling reaction



**Scheme 83**

We have also synthesized the sarcosine ester **367** (Scheme 86) and performed the Ireland Claisen rearrangement on this substrate with interesting results. Even though the

rearrangement is not stereospecific we are able to achieve epimerization from a 9:1 mixture favoring the wrong isomer to a 1:1 mixture. Such an intermediate would contain the methyl group on the nitrogen and the intent is to prevent any problems we could encounter later on in the synthesis with the glycine analog in terms of methylating the nitrogen.

## CHAPTER 5 EXPERIMENTAL SECTION

### General Procedure

All non-hydrolytic reactions were carried out under a nitrogen or argon atmosphere, with standard techniques for the exclusion of moisture. Glassware used for moisture sensitive reactions was flame dried with an internal inert gas sweep. Analytical TLC was performed on Whatman K6F silica gel 60A plates. Flash chromatography was performed on chromatographic silica gel, 230-400 mesh (Fisher Chemical). Infrared spectra were recorded on a Perkin-Elmer FT-IR (KBr). Proton, fluorine and carbon NMR spectra were obtained on a Varian 300MHz spectrometer using  $\text{CDCl}_3$ / TMS unless otherwise indicated in the experimental section or in the case of fluorine NMR spectra, a  $\text{CFCl}_3$  standard was utilized. Proton chemical shifts are reported in parts per million (ppm) relative to chloroform (7.24 ppm) or  $\text{DMSO-d}_6$  (2.49 ppm). Carbon chemical shifts are reported in parts per million relative to the central line of the  $\text{CDCl}_3$  triplet (77.0 ppm) or the central line of the  $\text{DMSO-d}_6$  septet (39.7 ppm). Coupling constants ( $J$ ) are given in Hz. Optical rotations were recorded on a Perkin-Elmer 241 digital polarimeter ( $10^{-1}$  deg.  $\text{cm}^2 \text{ g}^{-1}$ ). Melting points were obtained on a Thomas-Hoover capillary melting point apparatus. High resolution mass spectra and elemental analyses were performed at the University of Florida and Atlantic Microlab Inc.

Experimental Procedures3-(2,3-dimethoxyphenyl)-(1S,2R)-3-cyclohexene-1,2-diol (270).

To a round bottom flask under argon atmosphere was added Pd(PPh<sub>3</sub>)<sub>4</sub> (0.001 mol, 1.32g). This was followed by addition of 50 mL dry benzene. A solution of the bromide **247** (0.040 mol, 7.40 g) dissolved in 10mL of ethanol was then added to the reaction flask. This was followed by the addition of Na<sub>2</sub>CO<sub>3</sub> (36.00 mL, 2.00 M) to the mixture. Dimethoxyphenyl boronic acid **273** (0.046 mol, 8.40g) was dissolved in 50 ml of dry benzene was then added to the reaction mixture, which was allowed to reflux for 6h. The reaction was quenched with water and the product extracted with ethyl acetate (3 X 50 mL). The organic layers were combined, washed with brine and dried over anhydrous MgSO<sub>4</sub>. After filtration the solvent was removed, the crude product introduced onto a silica gel column, and eluted with ethyl acetate:hexane (1:3) to obtain (7.10 g, 83%) white crystals of **270**; mp: 66 - 67° C; Rf = 0.3 (ethyl acetate: hexane, 1:1); [α]<sub>D</sub><sup>20</sup> - 62.9 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.0 (t, J = 17.7 Hz, 1H), 6.9 (d, J = 7.1 Hz, 1H), 6.8 (dd, J = 7.4, 0.8 Hz, 1H), 5.9 (t, J = 3.6 Hz, 1H), 4.4 (bs, 1H), 3.9-3.8 (m, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 2.6 (bs, 2H), 2.3 (m, 2H), 1.9 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 152.5, 145.8, 136.6, 135.8, 130.5, 124.5, 122.5, 111.6, 69.3, 69.0, 61.0, 55.8, 25.2, 24.2, ; IR (KBr/ cm<sup>-1</sup>): 1104, 1260, 1470, 1577, 2923, 3362; LRMS (CI/ CH<sub>4</sub>) m/z (rel. intensity) 250 (m<sup>+</sup>, 100), 232 (35), 206 (93); HRMS Calcd. for C<sub>14</sub>H<sub>18</sub>O<sub>4</sub>: 250.1205; Found: 250.1208. Anal. Calcd. for C<sub>14</sub>H<sub>18</sub>O<sub>4</sub>: C, 67.21; H, 7.20; Found: C, 66.62; H, 7.44.

**6-(2,3-dimethoxyphenyl)-2-dimethylhexysilyoxy-(1R,2S)-5-cyclohexen-1-ol (276).**

A solution of the diol **270** (0.720 mmol, 0.18 g) and imidazole (0.860 mmol, 0.15 g) dissolved in 0.50 mL of DMF was prepared in a dry round bottom flask under argon atmosphere. The flask was cooled to -12° C and TDSCl (0.860 mmol, 0.17 mL) added with very slow stirring. The flask was stored at -18° C for 12h after which the solution was diluted with ethyl ether and washed with brine. After separation the aqueous layer was re-extracted with ethyl ether (2 X 20 mL). The organic layers were combined and washed with a 10% CuSO<sub>4</sub> solution (3 X 5 mL) to remove the imidazole. The organic layer was finally washed with brine, dried over anhydrous MgSO<sub>4</sub> and the solvent evaporated. The crude product was introduced unto a silica gel column and eluted with ethyl acetate/ hexane (1: 99) to afford a yellow oil of the silyl ether **276** (0.25 g, 90%); Rf = 0.7 (ethyl acetate :hexane, 1:4; [α]<sub>D</sub><sup>32</sup> - 59.3 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.0 (t, J = 7.2 Hz, 1H), 6.8 (d, J = 7.7 Hz, 2H), 5.9 (t, J = 3.6 Hz 1H), 4.4 (bs, 1H), 4.0 (dt, J = 10.2, 3.3 Hz, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 2.6 (d, J = 4.1 Hz, 1H), 2.4 - 2.3 (m, 1H), 2.2 - 2.1 (m, 1H), 2.0 - 1.9 (m, 1H), 1.7 - 1.6 (m, 2H), 0.9 - 0.8 (m, 14H), 0.1 (d, J = 5.5 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 152.6, 136.3, 136.0, 129.7, 123.9, 122.4, 111.4, 70.8, 69.2, 60.6, 55.8, 34.2, 25.4, 24.9, 24.3, 20.4, 20.2, 20.1, 18.6, 18.5, - 2.5, - 2.9; IR (KBr/cm<sup>-1</sup>): 3245, 2959, 1470, 1259, 1108, 1011. HRMS: C<sub>22</sub>H<sub>36</sub>O<sub>4</sub>Si (M+1) Calcd. 393.2383, Found: 393.2479; Anal. Calcd. for: C<sub>22</sub>H<sub>36</sub>O<sub>4</sub>Si: C, 67.18; H, 7.25; Found: C, 67.20 ; H, 7.24 .

6-(2,3-dimethoxyphenyl)-2-dimethylhexysilyloxy-(1*R*,2*S*)-5-cyclohexen-1-yl-*N*-*tert*-butoxycarbonyl glycinate (277).

A solution of Boc-glycine (6.600 mmol, 0.16 g) and DMAP (catalytic) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was cooled to 0° C. DCC (9.000 mmol, 1.90 g) was added to the cooled mixture resulting in a yellow precipitate. A solution of the TDS protected diol 276 (6.000 mmol, 2.20 g) in CH<sub>2</sub>Cl<sub>2</sub> was then added by syringe and the reaction mixture allowed to stir. The solution was diluted with ethyl ether and filtered through a plug of silica gel to remove the precipitate of dicyclohexylurea. Removal of the solvent followed by chromatography (silica gel, ethyl acetate:hexanes, 1:9) the residue afforded the pure amino ester 277 (4.00 g, 71%) as a thick colorless oil; R<sub>f</sub> = 0.4 ethyl acetate:hexane 80:20; [α]<sub>D</sub><sup>25</sup> -74.0 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 6.9 (t, J = 7.9 Hz, 1H), 6.8 (dd, J = 8.2 Hz, 1H), 6.7 (dd, J = 7.6 Hz, 1H), 5.9 (bs, 2H), 4.9 (bs, 1H), 4.1 (m, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 2.2 – 2.1 (m, 2H), 1.9 (m, 1H), 1.7 -1.6 (M, 1H), 1.6 - 1.5 (m, 1H), 1.4 (s, 9H), 0.9 (d, J = 6.7 Hz, 6H), 0.8 (d, J = 3.7 Hz, 6H), 0.1 (d, J = 11.9 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 168.4, 155.2, 154.1, 150.2, 134.6, 130.8, 130.6, 129.0, 128.9, 119.8, 110.3, 79.4, 71.7, 69.1, 54.3, 42.3, 34.2, 28.2, 25.0, 24.8, 24.4, 20.2, 20.1, 18.4, 18.3, -3.2; IR (KBr/cm<sup>-1</sup>): 3443, 2931, 2105, 1643, 1470, 1366; HRMS: C<sub>29</sub>H<sub>48</sub>NO<sub>7</sub>Si (M+) Calcd. 550.5983, Found: 550.3197. Anal. Calcd. for: C<sub>29</sub>H<sub>47</sub>NO<sub>7</sub>Si: C, 67.30; H, 9.24; Found: C, 67.13 ; H, 9.20 .

3-tert-butoxycarbonylamino-7a-(2,3-dimethoxyphenyl)-3S,3aS,7aS)-2,3,3a,4,5,7,7a-hexahydro[b]furan-2-one (279):

To the crude epimeric mixture of amino acids **278** (0.50 mmol, 0.30 g) was added a catalytic amount of *p*-TsOH in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and allowed to stir overnight. The reaction mixture was diluted with ethyl ether and washed with NaHCO<sub>3</sub> solution (30 %, 2 X 10 mL). The organic layer was dried with MgSO<sub>4</sub> and the solvent evaporated under reduced pressure. The lactone (**279**) was successively separated by column chromatography *via* gradient elution (hexanes: ethyl acetate, 99:1 - 9:1) to yield white crystals of A (0.10 g, 65 %); R<sub>f</sub> = 0.5 (ethyl acetate: hexanes, 1:4); [α]<sub>D</sub><sup>32</sup> - 96.0 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.1 -6.9 (m, 2H), 6.8 -6.7 (m, 2H), 6.2 (m, 1H), 5.7 (dt, J = 10.0, 1.0 Hz, 1H), 4.9 (d, J = 5.7 Hz, 1H), 4.5 (dd, J = 7.9, 3.0 Hz, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 3.3 (dtd, J = 11.5, 3.5, 1.0 Hz, 1H), 2.3 -2.2 (bm, 2H), 1.7 - 1.6 (m, 1H), 1.4 (s, 1H), 1.3 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 174.9, 155.3, 153.4, 135.1, 132.5, 126.9, 123.6, 117.2, 112.9, 82.8, 80.3, 59.9, 55.8, 54.1, 42.9, 29.7, 28.2, 22.8, 20.5; IR (KBr/ cm<sup>-1</sup>): 2932, 2253, 1776, 1716, 1506, 1475, 1263; LRMS (CI/ CH<sub>4</sub>) *m/z* (rel. intensity) 389 (m<sup>+</sup>, 70), 334 (65), 228 (100); HRMS Calcd. for C<sub>22</sub>H<sub>36</sub>NO<sub>6</sub> (m+1) Calcd.: 389.2464; Found: 389.5326. Anal Calcd. for C<sub>23</sub>H<sub>35</sub>NO<sub>6</sub>: C, 64.70; H, 6.90; Found: C, 64.36; H, 6.64.

6-(2,3-dimethoxyphenyl)-2-dimethylsilyloxy-(1*S*,2*R*)-5-cyclohexen-1-yl-N-phthaloylglycinate (285):

A solution of phthaloyl-glycine (1.40 mmol, 0.30 g), DCC (2.50mmol, 0.50 g), DMAP (catalytic) in dichloromethane (10 mL/mmol) was cooled to 0° C and a solution of the TDS protected diol **276** (1.20 mmol, 0.50 g) in dichloromethane (2 mL) was added. The cloudy reaction mixture was stirred overnight while it was allowed to reach room temperature. The solution was diluted with ethyl ether and filtered through a bed of silica gel to remove the precipitate of dicyclohexylurea. Removal of the solvent and chromatography (silica gel, ethyl acetate:hexanes, 9:1) of the residue, afforded the pure phthaloyl glycinate **285** as white crystals (0.35 g, 70%); R<sub>f</sub> = 0.8 (ethyl acetate: hexanes, 1:4); mp: 89 - 91° C; [α]<sub>D</sub><sup>25</sup> −79.7 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.81 (m, 2H), 7.65 (m, 2H), 6.90 (t, J = 7.9 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.49 (d, J = 7.9 Hz, 1H), 5.89 (t, J = 3.4 Hz, 1H), 5.85 (d, J = 2.8 Hz, 1H), 4.12 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.39-2.15 (m, 2H), 1.91-1.50 (m, 2H), 0.88 (dd, J = 6.7, 1.2 Hz, 6H), 0.84 (s, 7H), 0.12 (d, J = 5.8 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 168.80, 167.61, 153.32, 147.42, 135.00, 134.74, 133.93, 132.84, 124.40, 124.10, 122.84, 112.71, 73.43, 69.05, 60.93, 56.18, 39.10, 26.21, 25.11, 24.51, 20.41, 20.24, 18.74, 18.62, 9.37, -2.97; IR (KBr/ cm<sup>-1</sup>): 2954, 1752, 1726, 1470, 1416, 1205, 1114, HRMS Calcd. for C<sub>32</sub>H<sub>41</sub>NSiO<sub>4</sub> (M+): 579.2652; Found: 579.2652. Anal. Calcd. for C<sub>32</sub>H<sub>41</sub>NSiO<sub>4</sub>: C, 63.36; H, 8.62; Found: C, 63.51; H, 8.51.

6-bromo-2-dimethylsilyloxy-(1S,2R)-5-cyclohexen-1-yl-N-tert-butoxycarbonyl glycinate (292).

A solution of Boc-glycine (0.07 mol, 12.00 g), DCC (0.09 mol, 18.50 g), DMAP (catalytic) in dichloromethane (200 mL) was cooled to 0° C and a solution of the TDS protected diol **291** (0.045 mol, 15.00 g) in dichloromethane (200 mL) was added. The cloudy reaction mixture was stirred overnight while it was allowed to reach room temperature. The solution was diluted with ethyl ether and filtered through a bed of silica gel to remove the precipitate of dicyclohexylurea. Removal of the solvent and chromatography (silica gel, ethyl acetate:hexanes, 1:9) of the residue, afforded the pure glycinate (**292**) as a colorless oil (15.40 g, 70%); R<sub>f</sub> = 0.7 (ethyl acetate:hexanes, 1:4); mp: 89 - 91° C; [α]<sub>D</sub><sup>26</sup> -64.0 (c 1.0, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 6.27 (dd, J = 5.2, 3.1 Hz, 1H), 5.59 (d, J = 3.9 Hz, 1H), 5.00 (bs, 1H), 3.97 (m, 3H), 2.39-2.19 (m, 1H), 2.15-2.09 (m, 1H), 1.85-1.62 (m, 2H), 1.43 (s, 9H), 0.84 (s, 3H), 0.82 (s, 3H), 0.77 (d, J = 1.9 Hz, 6H), 0.07 (d, J = 4.6 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 169.59, 155.29, 134.80, 116.96, 79.64, 73.88, 69.23, 42.33, 34.03, 28.21, 25.49, 24.70, 22.55, 20.01, 18.48, -3.09, -3.15; IR (CHCl<sub>3</sub>/ cm<sup>-1</sup>): 3445, 2958, 1755, 1715, 1511, 1372; HRMS Calcd. for C<sub>21</sub>H<sub>39</sub>NsiBrO<sub>5</sub> (M+H): 492.1781; Found: 492.1806; Anal. Calcd. for: C<sub>21</sub>H<sub>38</sub>NsiBrO<sub>5</sub>: C, 51.21; H, 7.78; Found: C, 51.41; H, 7.75.

2-(4-dimethylhexylsilyloxy-2-bromo-(1S,4R)-2-cyclohexenyl-2R-N-tert-butoxycarbonylmethylglycinate (289a):

A solution of the glycine ester **292** (12.50 mmol, 6.23 g) in THF (100 mL) and a 1.0 M solution of ZnCl<sub>2</sub> (13.70 mmol, 13.70 mL) in ether was cooled to -78°C. Then a 1.7 M solution of LDA (31.00 mmol, 19.00 mL) in THF was added dropwise to the reaction mixture and the system allowed to warm to room temperature slowly (overnight). The reaction was quenched with water and the basic solution diluted with ethyl ether. The reaction mixture was then acidified slowly with HCl (1N) until a pH of approximately 2.5 was reached. After extraction with ethyl ether (3 X 100 mL) and drying with Na<sub>2</sub>SO<sub>4</sub>, the solvent was removed to afford the crude rearranged amino acids as light yellow crystals. The acids were purified by silica gel chromatography using a gradient elution of ethyl acetate: hexanes (1:6) followed by methanol (100%) to afford the mixture of acids. The mixture then treated with diazomethane to obtain the corresponding methyl esters. The epimeric methyl esters were then introduced unto a silica gel column and separated with hexanes (100%) to obtain clear oil of **289a** (2.33 g 38%); R<sub>f</sub> = 0.7 (ethyl acetate: hexanes, 1:4); [α]<sub>D</sub><sup>26</sup> -55.7 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 6.30 (dd, J = 5.6, 1.3 Hz, 1H), 5.21 (d, J = 8.6 Hz, 1H), 4.68 (dd, J = 8.7, 2.3 Hz, 1H) 4.11 (m, 1H), 3.71 (s, 3H), 3.05 (bs, 1H), 1.86-1.78 (m, 2H), 1.63-1.50 (m, 2H), 1.43 (s, 9H), 0.84 (d, J = 6.9 Hz, 6H), 0.80 (s, 6H), 0.05 (d, J = 5.3 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 171.85, 155.41, 136.30, 125.51, 80.02, 66.68, 55.86, 52.33, 45.13, 34.15, 29.16, 28.30, 25.76, 24.73, 23.40, 20.18, 18.56, -2.67, -2.88; IR (KBr/ cm<sup>-1</sup>): 3439, 2955, 2867, 1753, 1720, 1498, 1365, 1251, 1164; HRMS Calcd. for C<sub>20</sub>H<sub>36</sub>NsiBrO<sub>5</sub> (M+):

506.1920; Found: 506.1937; Anal. Calcd. for  $C_{20}H_{35}NSiBrO_4$ : C, 52.16; H, 7.96; Found: C, 52.28; H, 8.06. Structure was confirmed by X-ray Crystallography (Figure 7, pg 76).

2-(4-dimethylhexylsilyloxy-2-bromo-(1S,4R)-2-cyclohexenyl-2S-N-*tert*-butoxycarbonylmethylglycinate (289b):

The epimeric methyl esters were then introduced unto a silica gel column and separated with straight hexanes to obtain clear oil of **289b** (2.00 g 30%);  $R_f = 0.65$  (ethyl acetate:hexanes, 1:4);  $[\alpha]_D^{32} -27.7$  (c 1.0,  $CHCl_3$ );  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 6.17 (dd,  $J = 5.6, 1.3$  Hz, 1H), 4.85 (m, 2H), 4.12 (m, 1H), 3.74 (s, 3H), 2.96 (bs, 1H), 1.86-1.76 (m, 1H), 1.63-1.50 (m, 3H), 1.42 (s, 9H), 0.87 (d,  $J = 6.9$  Hz, 6H), 0.82 (s, 6H), 0.05 (d,  $J = 5.3$  Hz, 6H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$ : 171.86, 155.46, 135.56, 127.99, 79.86, 65.49, 55.34, 52.38, 43.84, 34.24, 29.58, 28.29, 24.87, 20.31, 19.99, 18.58, -2.47, -2.92; IR (KBr/  $cm^{-1}$ ): 3443, 2956, 2868, 1749, 1715, 1503, 1367, 1251, 1159; HRMS Calcd. for  $C_{20}H_{36}NSiBrO_5$  ( $M^+$ ): 506.1920; Found: 506.1937; Anal. Calcd. for  $C_{20}H_{35}NSiBrO_4$ : C, 52.16; H, 7.96; Found: C, 52.34; H, 8.01.

2-(4-dimethyl-*tert*-butylsilyloxy-2-bromo-(1*S*,4*R*)-2-cyclohexenyl-2*R*-N-*tert*-butoxycarbonylmethylglycinate (293):

A solution of the glycine ester **292** (13.40 mmol, 6.23 g) in THF (100 mL) and a 1.0 M solution of ZnCl<sub>2</sub> (21.10 mmol 20.00 mL,) in ether were cooled to -78°C. Then a 2.0 M solution of LDA (37.50 mmol, 19.00 mL) in THF was added dropwise to the reaction mixture and the system allowed to warm to room temperature slowly (overnight). The reaction was quenched with water and the basic solution diluted with ethyl ether. The reaction mixture was then acidified slowly with HCl (1N) until a pH of approximately 2.5 was reached. After extraction with ethyl ether (3 X 100 mL) and drying with Na<sub>2</sub>SO<sub>4</sub>, the solvent was removed to afford the crude rearranged amino acids as light yellow crystals. The acids were purified by silica gel chromatography using a gradient elution of ethyl acetate: hexanes (1:6) followed by methanol (100%). The pure acids were then treated with diazomethane to obtain the corresponding methyl esters. The epimeric methyl esters were then introduced unto a silica gel column and chromatographed with hexanes (100%) to obtain white crystal of **293** (2.63 g 40%); R<sub>f</sub> = 0.7 (ethyl acetate:hexanes, 1:4); mp: 115 - 117° C; [α]<sub>D</sub><sup>28</sup> -54.1 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 6.18 (dd, J = 5.6, 1.3 Hz, 1H), 5.23 (d, J = 8.6 Hz, 1H), 4.70 (dd, J = 8.7, 2.6 Hz, 1H) 4.13 (m, 1H), 3.72 (s, 3H), 3.09 (bs, 1H), 1.92-1.75 (m, 2H), 1.74-1.50 (m, 2H), 1.43 (s, 9H), 0.85 (s, 9H), 0.02 (d, J = 4.4 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 171.81, 155.37, 136.30, 125.62, 80.00, 66.78, 55.80, 52.29, 45.15, 29.14, 28.34, 28.20, 25.76, 25.67, 23.33, 17.95, -4.77; IR (KBr/ cm<sup>-1</sup>): 3394, 2963, 2857, 1733, 1710, 1645, 1522, 1365; HRMS Calcd. for C<sub>20</sub>H<sub>36</sub>NsiBrO<sub>5</sub> (M+): 478.1525; Found: 478.1525; Anal. Calcd. for C<sub>20</sub>H<sub>35</sub>NSiBrO<sub>4</sub>: C, 50.20; H, 7.58; Found: C, 50.15; H, 7.50.

2-(4-dimethylhexylsilyloxy-(1S,4R)-cyclohexyl)-2S-N-*tert*-butoxycarbonylmethyl glycinate (294).

To vinyl bromide **293** (0.20 mmol, 0.10 g) dissolved in benzene (10 mL) was added *n*-Bu<sub>3</sub>SnH (0.22 mmol, 0.06 g). This mixture was refluxed for approximately 30 min then AIBN (catalytic) was added and the reaction allowed to reflux for another 3 h. The reaction was quenched with water and the product extracted with ethyl acetate 3 X 10 mL. The organic layers were combined and dried over anhydrous MgSO<sub>4</sub>. After filtration the solvent was removed under reduced pressure and the solid residue introduced onto a silica gel column and eluted with ethyl acetate: hexanes (1:6), to obtain **294** (0.07 g, 82%) as a light yellow oil; R<sub>f</sub> = 0.75 (ethyl acetate:hexanes, 1:6); [α]<sub>D</sub><sup>28</sup> = 14.9 (c 1.0, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.85 (m, 1H), 5.46 (d, J = 9.8 Hz, 1H), 4.93 (d, J = 8.9 Hz, 1H), 4.29 (dd, J = 8.9, 3.8 Hz), 4.06 (d, J = 3.7 Hz, 1H), 3.71 (s, 3H), 2.61 (bs, 1H), 1.76-1.67 (m, 2H), 1.63-1.54 (m, 4H), 1.41 (s, 9H), 0.86 (d, J = 6.7 Hz, 6H), 0.80 (s, 7H), 0.06 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 172.87, 156.08, 134.12, 127.27, 112.56, 80.17, 63.73, 57.15, 52.59, 38.15, 34.31, 30.54, 28.24, 27.22, 24.73, 20.63, 20.35, 20.26, 18.57, -2.07, -2.43. IR (CHCl<sub>3</sub>/ cm<sup>-1</sup>): 3448, 2958, 1755, 1710, 1522, 1365; HRMS Calcd. for C<sub>22</sub>H<sub>42</sub>NSiO<sub>5</sub> (M+1): 427.6600; Found: 427.6812; Anal. Calcd. for: C<sub>22</sub>H<sub>41</sub>NSiO<sub>5</sub>: C, 61.79; H, 9.66; Found: C, 61.77; H, 9.71.

2-(4-dimethylhexylsilyloxy-2-Cyclohexenyl)-2R-N-*tert*-butoxycarbonylmethylglycinate (295)

To vinyl bromide **293** (0.70 mmol, 0.34 g) was added to a mixture of catalytic amount of Adams Catalyst, triethylamine (0.70 mmol, 0.73 mL) and methanol (5.0 mL). The reaction vessel was evacuated and the solution stirred under hydrogen atmosphere (40 psi) for 3h. After completion of the reaction (as observed by TLC), the suspension was filtered and the solvent concentrated under reduced pressure. The solid residue was diluted with ethyl acetate (10 mL) and washed with water (2 X 2 mL), followed by NaHCO<sub>3</sub> (2 X 2 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford white crystals of **295** (0.30 g, 89%); Rf = 0.65 (ethyl acetate:hexanes, 1:6); [α]<sub>D</sub><sup>26</sup> -4.9 (c 1.0, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.05 (d, J = 9.1 Hz, 1H), 4.22 (q, J = 4.5 Hz, 1H), 3.93 (bs, 1H), 3.70 (s, 3H), 1.78-1.44 (m, 8H), 1.41 (s, 9H), 0.88 (d, J = 6.4 Hz, 6H), 0.81 (s, 7H), 0.02 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 172.77, 155.42, 79.51, 65.68, 57.90, 51.95, 40.45, 34.39, 32.90, 28.27, 24.74, 22.86, 21.63, 20.29, 18.62, -3.04; IR (CDCl<sub>3</sub>/cm<sup>-1</sup>): 3440, 2929, 1755, 1712, 1503, 1162; HRMS Calcd. for C<sub>22</sub>H<sub>44</sub>NSiO<sub>5</sub> (M+1): 430.2922; Found: 430.2988; Anal. Calcd. for: C<sub>22</sub>H<sub>43</sub>NSiO<sub>5</sub>; C, 61.50; H, 10.09; Found: C, 61.57; H, 10.12.

2-(4-hydroxy-2-cyclohexenyl)2R)-2R-N-tertbutoxycarbonylmethyl glycinate (296)

To a solution of the ester **295** (0.800 mmol, 0.450 g) in THF (10 mL) was added distilled TBAF (1.600 mmol, 1.60 mL). The mixture was stirred for 3h and monitored by TLC. After consumption of starting material the solvents were removed and the solid residue introduced onto a silica gel column and eluted with ethyl acetate: hexanes (1:1) to afford white flaky crystals of the alcohol **296** (0.322 g, 90 %).  $R_f = 0.45$ , (ethyl acetate:hexanes 1:1);  $[\alpha]_D^{30} -4.2$  (c 1.0, MeOH);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 5.20 (s, 1H), 4.01 (bs, 1H), 3.84 (s, 3H), 3.59 (s, 3H), 1.82 - 1.42 (m, 8H), 1.41 (s, 9H), 1.39 – 1.20 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 173.73, 160.36, 79.94, 74.22, 58.49, 52.18, 41.24, 29.65, 28.54, 28.55, 28.33, 21.31, 26.17; IR (NaCl/ cm $^{-1}$ ): 3440, 3377, 2929, 2855, 1743, 1712, 1162; HRMS Calcd. for  $\text{C}_{14}\text{H}_{25}\text{NO}_5$  (m+H – H<sub>2</sub>O): 271.3645; Found: 271.4012.

2-(2-Cyclohexenyl)-2R-N-*tert*-butoxycarbonylmethylglycinate (304):

To vinyl bromide **293** (0.10 g, 0.20 mmol) was added to a mixture of catalytic amount of 10% Pd-C and methanol (1.0 mL). The reaction vessel was evacuated and the solution stirred under hydrogen atmosphere (15 psi) for 1h. After completion of the reaction (as observed by TLC), the suspension was filtered and the solvent concentrated under reduced pressure. The solid residue was recrystallized from Ethyl acetate/ Hexanes to give the ester **304** (0.04 g, 75%) as a white solid; Rf = 0.8 (ethyl acetate:hexanes 1:6); mp: 110 -112 °C;  $[\alpha]_D^{25} -19.7$  (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.00 (d, J = 8.1 Hz, 1H), 4.18 (dd, J = 8.5, 5.1 Hz, 1H), 3.71 (s, 3H), 1.81-1.56 (m, 10H), 1.41 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 173.15, 155.81, 79.94, 58.49, 52.18, 41.24, 29.65, 28.54, 28.50, 28.33, 26.17; IR (KBr/ cm<sup>-1</sup>): 3420, 2950, 1755, 1712, 1503, 1180; HRMS Calcd. for C<sub>14</sub>H<sub>25</sub>NO<sub>4</sub>: 271.2434; Found: 271.2814.

6-Bromo-2-dimethylhexysilyloxy-(1S,2R)-5-cyclohexen-1-yl-N-tert-  
alanylcarbonylglycinate (301).

A solution of N-Boc-alanine (6.600 mmol, 0.30 g), DCC (9.00mmol, 1.90 g), DMAP (catalytic) in dichloromethane (10 mL/mmol) was cooled to 0° C and a solution of the TBS protected diol **298** (6.000 mmol, 2.20 g) in dichloromethane (40 mL) was added by syringe and the reaction mixture stirred overnight while it was allowed to reach room temperature. The solution was diluted with ethyl ether and filtered through a bed of silica gel to remove the precipitate of dicyclohexylurea. Removal of the solvent and chromatography (silica gel, hexanes:ethyl acetate, 90:10) of the residue, afforded the pure ester as a light yellow oil (2.40 g, 71%); Rf = 0.5 ethyl acetate :hexanes, 1:6; [α]<sub>D</sub><sup>28</sup> = 68.1 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 6.26 (dd, J = 2.6, 5.1 Hz, 1H), 5.53 (d, J = 3.9 Hz, 1H), 5.13 (d, J = 8.1 Hz, 1H), 4.40 (q, J = 7.2 Hz, 1H), 3.94 (dt, J = 3.7 Hz, 1H), 2.32-2.01 (m, 1H), 1.83-1.62 (m, 2H), 1.45 (s, 3H), 1.43 (s, 9H), 0.82 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 172.49, 157.77, 134.67, 1171.71, 79.36, 73.73, 69.37, 67.85, 49.12, 28.24, 25.79, 24.51, 25.64, 25.60, 25.55, 19.15, 18.01, -5.08, -5.17; IR (KBr/ cm<sup>-1</sup>): 3435, 2952, 2928, 2855, 1747, 1714, 1649, 1163; HRMS Calcd. for C<sub>20</sub>H<sub>36</sub>BrNSiO<sub>5</sub> (M+): 478.1636; Found: 478.1624. Anal. Calcd. for C<sub>20</sub>H<sub>36</sub>BrNSiO<sub>54</sub>: C, 50.20; H,7.58; Found: C, 50.19; H, 7.64.

6-bromo-2-dimethyltert-butylsilyloxy-(1S,2R)-5-cyclohexen-1-yl alanine(302).

A solution of the alanine ester **301** (10.00 mmol, 4.80 g) in CH<sub>2</sub>Cl<sub>2</sub> (250 mL) was cooled to 0°C. Freshly distilled TFA (18.10 mmol, 9.60 mL) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was then added dropwise over 30 min. The mixture was stirred for 3h and monitored by TLC. After consumption of starting material the reaction was quenched with NaHCO<sub>3</sub> (saturated). The phases were separated and the organic layer washed with brine. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give white flaky crystals of the free amine **302** (2.84 g, 75%). R<sub>f</sub> = 0.74, (ethyl acetate 100%); [α]<sub>D</sub><sup>30</sup> = -59.1 (c 1.0, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.50-7.71 (bs, 2H), 6.28 (dd, J = 3.6, 4.5 Hz, 1H), 5.57 (d, J = 3.6 Hz, 1H), 4.09 – 3.97 (m, 2H), 2.34 - 2.24 (bm, 1H), 2.12 – 1.98 (bm, 2H), 1.84 - 1.70 (m, 2H), 1.66 (d, J = 7.1, 3H), 0.83 (s, 9H), 0.04 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 169.60, 135.53, 116.51, 75.57, 69.28, 49.26, 26.21, 25.84, 25.71, 18.33, 16.27, -4.81, -4.96; IR (NaCl/ cm<sup>-1</sup>): 3434, 3377, 2953, 2929, 2856, 1752, 1677, 1203, 1136; HRMS Calcd. for C<sub>15</sub>H<sub>28</sub>BrNO<sub>3</sub>Si (m+): 378.3853; Found: 378.1100.

6-bromo-2-dimethyltert-butylsilyloxy-(1S,2R)-5-cyclohexen-1-yl-N-1-phenyl-(4'-methoxy-4-phenyl)-alanyl sulfonamide (299).

To a solution of amine **302** (0.530 mol, 0.200 g), in THF (10 mL) was added Et<sub>3</sub>N (0.800 mmol, 0.080 g). To this mixture was added the sulfonyl choride (0.080 mmol, 0.218 g) and the reaction mixture stirred for 48h. The reaction mixture filtered through a bed of silica gel followed by removal of the solvent and chromatography (silica gel, ethyl acetate:hexanes, 1:8) of the residue, afforded the pure sulfonamide **299** as a white crystalline solid (0.132 g, 40%); R<sub>f</sub> = 0.4 (ethyl acetate:hexanes, 1:4); mp: 114 – 116; [α]<sub>D</sub><sup>28</sup> – 44.0 (c 1.0, CHCl<sub>3</sub>): <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.87 (m, 2H), 7.62 (m, 2H), 7.50 (m, 2H), 6.97 (m, 2H), 6.20 (m, 1H), 5.41 (m, 2H), 4.10 (m, 1H) 3.85 (s, 3H), 2.23 - 2.16 (m, 1H), 2.10 – 1.90 (m, 1H), 1.68 - 1.61 (m, 2H), 1.56 (s, 3H), 1.51 - 1.49 (m, 4H), 1.20 (m, 1H), 0.77 (m, 9H), 0.82 (s, 3H), -0.02 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 170.88, 170.87, 160.01, 145.13, 138.17, 135.06, 131.63, 128.37, 127.69, 127.53, 116.64, 114.44, 74.49, 69.27, 55.37, 51.71, 26.29, 25.76, 25.63, 20.35, 18.06, -5.03, -5.14; IR (CHCl<sub>3</sub>/ cm<sup>-1</sup>): 3281, 2951, 2949, 2854, 1743, 1610, 1595, 1519, 1488, 1250; HRMS Calcd. for C<sub>28</sub>H<sub>39</sub>NsiBrO<sub>6</sub> (M+): 624.1451; Found: 625.1450.

(1S,4R)-2-cyclohexenyl-2S-N-1-phenyl-(4'-methoxy-4-phenyl)-alanyl sulfonamide  
(303).

A solution of the alanine ester **300** (0.800 mmol, 0.450 g) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was cooled to 0°C. Freshly distilled TFA (1.600 mmol, 1.50 mL) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was then added dropwise over 30 min. The mixture was stirred for 3h and monitored by TLC. After consumption of starting material the reaction was quenched with NaHCO<sub>3</sub> (saturated). The phases were separated and the organic layer washed with brine. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give white flaky crystals of the alcohol **303** (0.322 g, 90 %). R<sub>f</sub> = 0.4, (ethyl acetate:hexanes 1:1); [α]<sub>D</sub><sup>30</sup> -5.1 (c 1.0, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.86 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 5.41 (s, 1H), 5.20 (bs, 1H), 3.84 (s, 3H), 3.61 (s, 3H), 2.05 (bm, 2H), 1.82 - 1.42 (m, 8H), 1.41 (s, 3H), 1.39 – 1.20 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 173.73, 160.36, 156.65, 145.32, 140.09, 131.75, 128.63, 127.86, 127.15, 114.74, 74.22, 65.37, 55.63, 52.84, 45.83, 29.61, 29.46, 21.31, 21.05, 17.59; IR (NaCl/ cm<sup>-1</sup>): 3434, 3377, 2953, 2929, 2856, 1752, 1677, 1203, 1136; HRMS Calcd. for C<sub>15</sub>H<sub>28</sub>BrNO<sub>3</sub>Si (m+H – H<sub>2</sub>O): 430.1682; Found: 430.1688.

2-(4-dimethylhexylsilyloxy-2-(2-benzyloxy-3-methoxyphenyl)-(1S,4R)-2-cyclohexenyl-2S-N-*tert*-butoxycarbonylmethylglycinate (312).

To a two neck round bottom flask fitted with a condenser under an argon atmosphere was added Pd(PPh<sub>3</sub>)<sub>4</sub> (7.00 mmol, 0.010 g). This was followed by addition of dry benzene (15 mL). A solution of the vinyl bromide **289b** (0.350 mmol, 0.176 g) dissolved in benzene (5 mL) was then added to the reaction flask. This was followed by the addition of Na<sub>2</sub>CO<sub>3</sub> (2.0 M, 0.60 mL), to the mixture. Boronic acid **313** (0.26 mmol, 0.07g) dissolved in benzene (5 mL) was then added to the reaction mixture, which was allowed to reflux for 6h. The reaction was quenched with water and the product extracted with ethyl acetate (3 X 20 mL). The organic layers were combined, washed with brine and dried over anhydrous MgSO<sub>4</sub>. After filtration the solvent was removed, the crude product introduced onto a silica gel column, and eluted with ethyl acetate: hexanes (1/3) to obtain **312** (0.10 g, 70%) as a light yellow oil; R<sub>f</sub> = 0.35 (ethyl acetate: hexanes, 1:4); [α]<sub>D</sub><sup>29</sup> +26.7 (c 1.0, CDCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.31 (m, 5H), 6.95 (t, J = 7.8 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 6.58 (d, J = 7.3 Hz, 1H), 5.77 (d, J = 4.6 Hz, 1H) 5.02 (d, J = 11.2 Hz, 1H), 4.91 (d, J = 11.2 Hz, 1H), 4.82 (d, J = 7.3 Hz, 1H), 4.13 (m, 1H), 3.96 (q, J = 4.0 Hz, 1H), 3.85 (s, 3H), 3.62 (s, 3H), 3.46 (q, J = 7.0 Hz, 1H), 1.78-1.49 (m, 4H), 1.36 (s, 9H), 1.24-1.17 (m, 5H), 0.91 (d, J = 6.7 Hz, 6H), 0.86 (s, 7H), 0.11 (d, J = 8.5 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 172.46, 155.11, 152.24, 144.93, 139.82, 137.82, 135.16, 132.17, 128.16, 128.13, 127.66, 124.24, 122.04, 111.77, 79.19, 74.72, 63.37, 55.69, 54.64, 51.91, 38.48, 34.33, 29.82, 28.28, 27.96, 24.84, 20.38, 18.62, 18.35, 17.91, 15.23, -2.35, -2.87; IR (CDCl<sub>3</sub>/ cm<sup>-1</sup>): 3370, 2989, 2959, 1750, 1720, 1698, 1520, 1505, 1454; HRMS Calcd.for C<sub>36</sub>H<sub>53</sub>NO<sub>7</sub>Si (m+): 639.9104 ;Found: 639.9102.

2-(4-dimethylhexylsilyloxy-2-(2,3-dimethoxyphenyl)-(1S,4R)-2-cyclohexenyl-2S-N-tert-butoxycarbonylmethylglycinate (316).

To a two neck round bottom flask fitted with a condenser under an argon atmosphere was added Pd(PPh<sub>3</sub>)<sub>4</sub> (0.01 mmol, 0.014 g). This was followed by addition of dry benzene (15 mL). A solution of the vinyl bromide **289b** (0.400 mmol, 0.200 g) dissolved in benzene (5 mL) was then added to the reaction flask. This was followed by the addition of Na<sub>2</sub>CO<sub>3</sub> (2.0 M, 1.20 mL), to the mixture. Boronic acid **273** (0.600 mmol, 0.110 g) dissolved in benzene (5 mL) was then added to the reaction mixture, which was allowed to reflux for 6h. The reaction was quenched with water and the product extracted with ethyl acetate (3 X 20 mL). The organic layers were combined, washed with brine and dried over anhydrous MgSO<sub>4</sub>. After filtration the solvent was removed, the crude product introduced onto a silica gel column, and eluted with ethyl acetate: hexanes (1/3) to obtain **316** (0.10 g, 70%) as a light yellow oil; R<sub>f</sub> = 0.40 (ethyl acetate: hexanes, 1:4); [α]<sub>D</sub><sup>30</sup> +26.9 (c 1.0, CDCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 6.92 (t, J = 7.9 Hz, 1H), 6.81(d, J = 7.9 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 5.95 (d, J = 2.4 Hz, 1H), 5.23 (m, 1H), 4.33 (bs, 1H), 4.08 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.65 (s, 3H), 3.45 (bs, 1H), 1.94-1.63 (m, 4H), 1.56 (bs, 1H), 1.38 (s, 9H), 0.86 (m, 6H), 0.08 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 173.21, 155.65, 152.57, 146.46, 142.15, 134.83, 131.37, 124.49, 122.49, 112.31, 79.86, 63.93, 61.07, 56.17, 55.35, 52.59, 39.56, 30.45, 28.79, 19.16, -2.45, -2.71; IR (CDCl<sub>3</sub>/ cm<sup>-1</sup>): 3348, 2975, 2937, 1751, 1714, 1689, 1520, 1474, 1259, 1225, 1159, 1062, ; HRMS Calcd. for C<sub>30</sub>H<sub>49</sub>NO<sub>7</sub>Si (m+): 563.0491 ; Found: 563.0451.

2-(4-hydroxy-2-benzyloxy-3-methoxyphenyl)-(1S,4R)-2-cyclohexenyl-2S-N-*tert*-butoxycarbonylmethylglycinate (311):

To a solution of the silyl ether **312** (0.183 mmol, 0.177 g) in THF (10 mL) was added TBAF (0.220 mmol, 0.220 mL). This mixture was stirred for 3h while being monitored by TLC. The reaction mixture filtered through a bed of silica gel followed by removal of the solvent, trituration with CCl<sub>4</sub> (3 X 20 mL) and chromatography (silica gel, ethyl acetate: hexanes, 1:8) of the residue, afforded the pure alcohol **311** as a light yellow oil (0.061 g, 75%; Rf = 0.4 (hexanes:ethyl acetate, 1:1); [α]<sub>D</sub><sup>27</sup> + 52.7 (c 1.0, CHCl<sub>3</sub>): <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.32 (m, 4H), 6.95 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 5.79 (d, J = 3.7 Hz, 1H), 5.09 (d, J = 8.1 Hz, 1H), 5.05 – 4.90 (m, 2H), 4.19 – 4.07 (bm, 2H), 3.85 (s, 3H), 3.61 (s, 3H), 3.36 (bs, 1H), 1.79 (bs, 2H), 1.61 (m, 2H), 1.33 (s, 9H), 1.16 (bm, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 172.65, 155.17, 152.36, 145.02, 141.36, 137.96, 134.89, 131.01, 128.20, 127.76, 124.17, 121.93, 111.88, 79.38, 74.75, 63.53, 55.77, 54.89, 51.89, 39.16, 29.67, 28.28, 18.77; IR (CHCl<sub>3</sub>/ cm<sup>-1</sup>): 3350, 2964, 2934, 2359, 1749, 1713, 1517, 1469, 1365, 1258, 1216, 1158; HRMS Calcd. for C<sub>28</sub>H<sub>36</sub>NO<sub>7</sub> (M+ 1): 498.5900; Found: 498.2491.

2-(4-hydroxy-2-(2,3-dimethoxyphenyl)-(1S,4R)-2-cyclohexenyl-2S-N-*tert*-butoxycarbonylmethylglycinate (317)

To a solution of the silyl ether **316** (0.355 mmol, 0.200 g) in THF (10 mL) was added TBAF (0.533 mmol, 0.533 mL). This mixture was stirred for 3h while being monitored by TLC. The reaction mixture filtered through a bed of silica gel followed by removal of the solvent, trituration with CCl<sub>4</sub> (3 X 20 mL) and chromatography (silica gel, ethyl acetate: hexanes, 1:8) of the residue, afforded the pure alcohol **317** as a colorless oil (0.120 g, 81%; Rf = 0.4 (hexanes:ethyl acetate, 1:1); [α]<sub>D</sub><sup>27</sup> + 28.6 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ: 6.92 (t, J = 7.9 Hz, 1H), 6.81(d, J = 7.9 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 5.95 (d, J = 2.4 Hz, 1H), 5.23 (m, 1H), 4.33 (bs, 1H), 4.08 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.65 (s, 3H), 3.45 (bs, 1H), 1.94-1.63 (m, 4H), 1.56 (bs, 1H), 1.38 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 173.21, 155.65, 152.57, 146.46, 142.15, 134.83, 131.37, 124.49, 122.49, 112.31, 79.86, 63.93, 61.07, 56.17, 55.35, 52.59, 39.56, 30.45, 28.79, 19.16.; IR (CDCl<sub>3</sub>/ cm<sup>-1</sup>): 3348, 2975, 2937, 1751, 1714, 1689, 1520, 1474, 1259, 1225, 1159, 1062, ; HRMS Calcd. for C<sub>30</sub>H<sub>49</sub>NO<sub>7</sub>Si (m+): 421.4910 ; Found: 421.3720;

2-(4-benzoyl-2-(2-benzyloxy-3-methoxyphenyl)-(1S,4R)-2-cyclohexenyl-2S-N-*tert*-butoxycarbonylmethylglycinate (314):

To a stirred solution of the alcohol **311** (0.183 mmol, 0.091 g) and benzoic acid (0.366 mmol, 0.050 mL) in dry THF (5 mL) was added a solution of the Mitsunobu reagent previously prepared by addition of diethyl azodicarboxylate (DEAD) (0.366 mmol, 0.058 mL) to a stirred solution of  $\text{PBu}_3$  (0.366 mmol, 0.091 mL) in THF (5 mL) at 0°C and stirred at the same temperature for 15 min. The reaction mixture was allowed to warm slowly to room temperature over 3h after which the solvents were removed under reduced pressure an the crude product purified by chromatography (silica gel, ethyl acetate: hexanes, 1:8) of the residue, afforded the pure benzoate **314** as a clear oil (0.155 g, 94 %);  $R_f = 0.6$  (ethyl acetate :hexanes, 1:4) ;  $[\alpha]_D^{27} + 166.8$  (c 1.0,  $\text{CHCl}_3$ ):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.01 (m, 1H), 7.92 (d,  $J = 1.5$  Hz, 1H), 7.56 - 7.23 (m, 10H), 6.96 (t,  $J = 8.1$  Hz, 1H), 6.84 (d,  $J = 8.3$  Hz, 1H), 6.66 (d,  $J = 8.0$  Hz, 1H), 5.88 (m, 1H), 5.08 (d,  $J = 11.0$  Hz, 1H), 4.92 (d,  $J = 11.2$  Hz, 1H), 4.66 (d,  $J = 8.3$  Hz, 1H), 4.15 (bm, 2H), 3.85 (s, 3H), 3.59 (s, 3H), 3.57 (bs, 1H), 2.21( bm, 1H), 1.71 (bm, 2H), 1.35 (s, 9H), 1.21 (bm, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 172.65, 155.17, 152.36, 145.02, 141.36, 137.96, 134.89, 131.01, 128.20, 127.76, 124.17, 121.93, 111.88, 79.38, 74.75, 63.53, 55.77, 54.89, 51.89, 39.16, 29.67, 28.28, 18.77; IR ( $\text{CHCl}_3/\text{cm}^{-1}$ ): 3370, 2950, 1747, 1715, 1698, 1520, 1505, 1454; HRMS Calcd. for  $\text{C}_{35}\text{H}_{40}\text{NO}_8$  (m+): 602.2774; Found: 602.2754.

2-[4-oxo-2-(2-benzyloxy-3-methoxyphenyl)-(1S,4R)-2-cyclohexenyl-2S-N-*tert*-butoxycarbonylmethylglycinate (326):

To a solution of the alcohol **311** (0.603 mmol, 0.300 g) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added PCC (0.905 mmol, 0.200 g). This mixture was allowed to stir for 12h after which the reaction mixture was filtered through a bed of silica gel followed by removal of solvents. The crude product was chromatographed (silica gel, ethyl acetate: hexanes, 1:4) to afford the pure enone **326** as a light brown oil (0.250 g, 84%); R<sub>f</sub> = 0.6 (hexanes:ethyl acetate, 1:1); [α]<sub>D</sub><sup>27</sup> + 18.6 (c 1.0, CHCl<sub>3</sub>): <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.28 (m, 5H), 7.02 (t, J = 7.8 Hz, 1H), 6.93 (dd, J = 1.5 Hz, 1H), 6.65 (dd, J = 1.5 Hz, 1H), 5.87 (m, 1H), 4.98 (q, J = 11.4 Hz, 2H), 4.69 (m, 1H), 4.40 (bs, 1H), 3.89 (s, 3H), 3.63 (m, 1H), 3.56 (s, 3H), 2.52-2.46 (m, 1H), 2.28-2.18 (m, 1H), 1.84-1.73 (m, 2H), 1.32 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 198.29, 171.92, 160.74, 154.67, 152.39, 144.43, 137.21, 133.54, 130.98, 128.45, 128.27, 124.56, 121.27, 113.17, 79.81, 75.32, 55.84, 54.78, 52.22, 40.41, 35.24, 28.11, 23.94; IR (CDCl<sub>3</sub>/cm<sup>-1</sup>): 3342, 2951, 1747, 1706, 1676, 1471, 1454, 1366, 1264, 1213, 1158; HRMS Calcd.for C<sub>28</sub>H<sub>33</sub>NO<sub>7</sub> [(m+1)+ Na]: 518.2154 ; Found: 518.2160.

2-(4-dimethylhexylsilyloxy)-2-(2-hydroxy,3-dimethoxyphenyl)-(1S,4R)-2-cyclohexenyl-2S-N-*tert*-butoxycarbonylmethylglycinate (358):

To a two neck round bottom flask fitted with a condenser under an argon atmosphere was added Pd(PPh<sub>3</sub>)<sub>4</sub> (0.022 g, 0.019 mmol). This was followed by addition of dry benzene (10 mL). A solution of the vinyl bromide **289b** (0.640 mmol, 0.326 g) dissolved in benzene (5 mL) was then added to the reaction flask. This was followed by the addition of Na<sub>2</sub>CO<sub>3</sub> (2.0 M, 2.5 mL), to the mixture. Boronic acid **357** (0.600 mmol, 0.110 g) dissolved in a mixture of benzene (5 mL) and ethanol (1 mL) was then added to the reaction mixture, which was allowed to reflux for 6h. The reaction was quenched with water and the product extracted with ethyl acetate (3 X 20 mL). The organic layers were combined, washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration the solvent was removed, the crude product introduced onto a silica gel column, and eluted with ethyl acetate: hexanes (1/3) to obtain the coupled product **358** (0.158 g, 45%) as a light yellow oil; R<sub>f</sub> = 0.78 (ethyl acetate: hexanes, 1:1); [α]<sub>D</sub><sup>30</sup> (c 1.0, CDCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 6.75 (m, 2H), 6.67 (m, 1H), 5.93 (dd, J = 1.9, 5.0 Hz, 1H), 5.85 (bs, 1H), 4.86 (d, J = 7.8 Hz, 1H), 4.24 (m, 1H), 4.04 (dt, J = 4.2, 7.6 Hz, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.57 (bs, 1H), 1.74 (m, 2H), 1.65-1.62 (m, 2H), 1.35 (s, 9H), 0.91(dt, J = 1.7, 6.8 Hz, 6H), 0.86 (s, 6H), 0.12 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 172.70, 155.21, 146.24, 142.58, 138.68, 132.74, 126.51, 121.86, 119.77, 109.83, 79.28, 63.59, 55.93, 54.78, 52.09, 38.13, 34.39, 29.98, 28.28, 24.88, 20.43, 20.39, 18.67, 18.30, -2.36, -2.83; IR (CDCl<sub>3</sub>/ cm<sup>-1</sup>): 3448, 2955, 2868, 1752, 1721, 1520, 1472, 1279, 1159, 1065; HRMS Calcd.for C<sub>29</sub>H<sub>47</sub>NO<sub>7</sub>Si (m+): 549.7864 ; Found: 549.3122.

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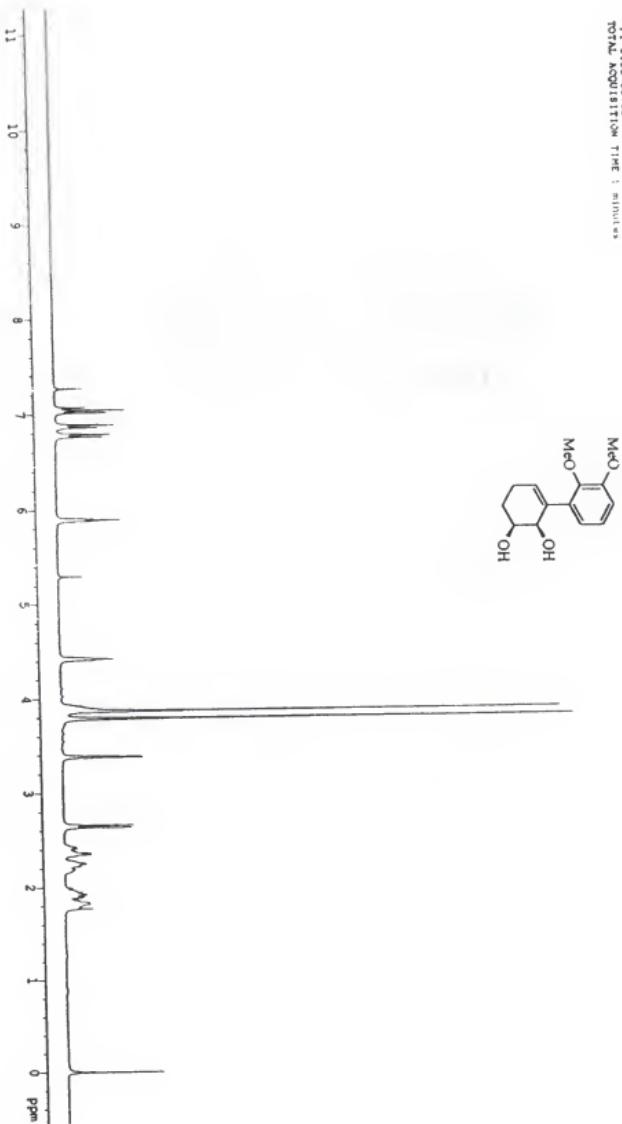
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APPENDIX  
SELECTED SPECTRA

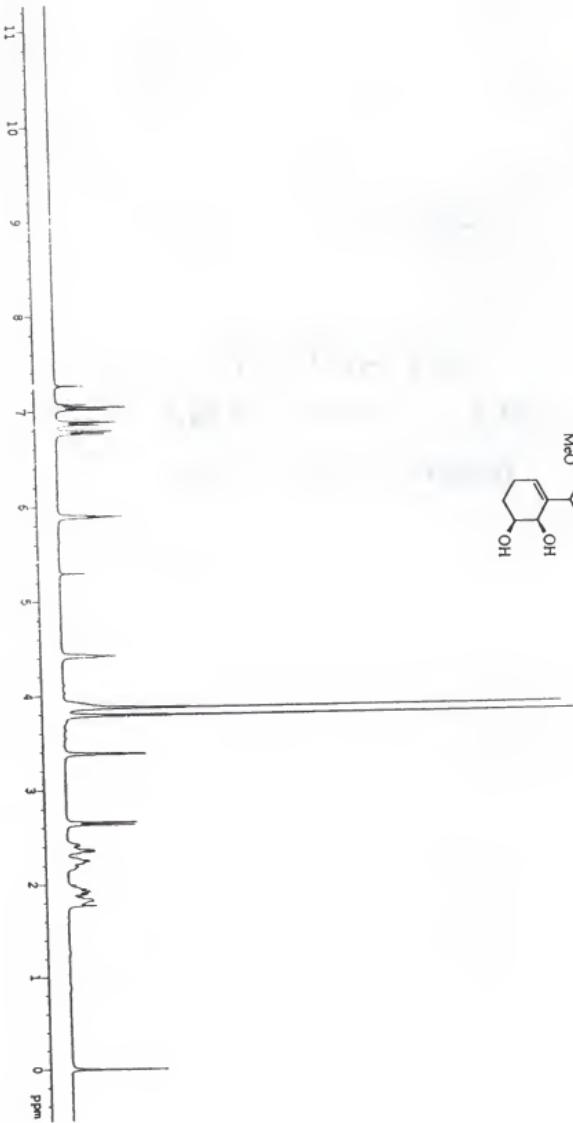
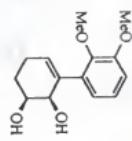
The  $^1\text{H}$  and  $^{13}\text{C}$  or APT NMR spectra of selected compounds reported in Chapter III and IV are graphically displayed in this appendix. The spectra along with the proposed structure are shown.

reduced diethoxyphenyl diol

ORIGINATE: HI  
FREQUENCY: 300.075 MHz  
SWEEP WIDTH: 1500.5 Hz  
ACQUISITION TIME: 1.998 sec  
RELAXATION DELAY: 0.000 sec  
PULSE WIDTH: 5.0 usec  
AMBIENT TEMPERATURE  
NO. REPETITIONS: 16  
DOUBLE PRECISION: NO  
DATA POINTS: 1024  
FT SIZE: 32.88 sec  
LINE BROADBANDING: 1.0 Hz  
TOTAL ACQUISITION TIME: 1 minute

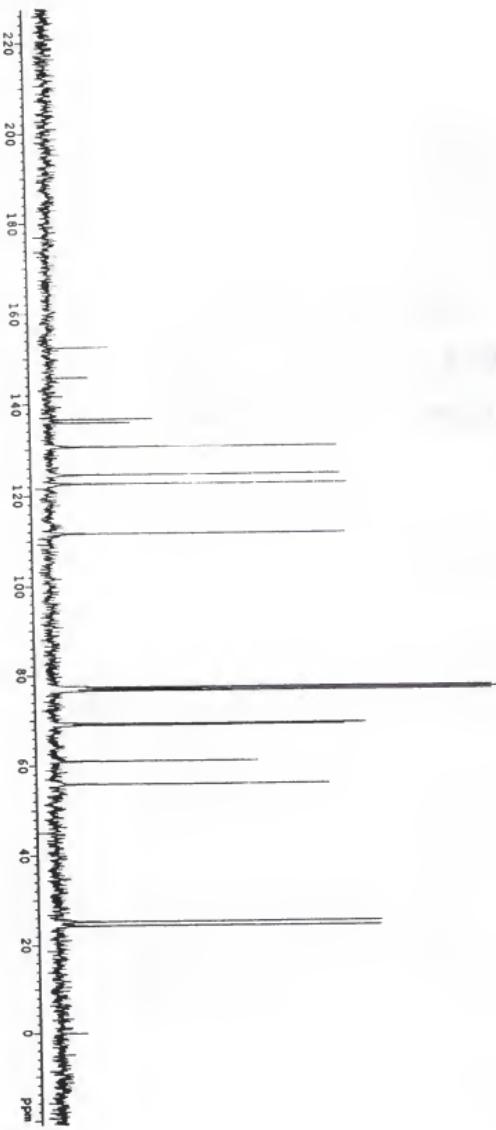


reduced dianethoxyphenyl diol  
Oxfordshire UK 300.075 MHz  
TELESCOPE 300.075 MHz  
SPECTRAL WIDTH 4000.5 Hz  
ACQUISITION TIME 1.598 sec  
RELAXATION DELAY 0.000 sec  
PULSE WIDTH 1.000 sec  
ROTATION SPLITTING 16 Hz  
NO. OF SPIN AVERAGES 16  
DOUBLE PRECISION ACQUISITION  
DATA PROCESSING  
LINE BROADENING 1.0 Hz  
FT SIZE 27360  
TOTAL ACQUISITION TIME 1 minute

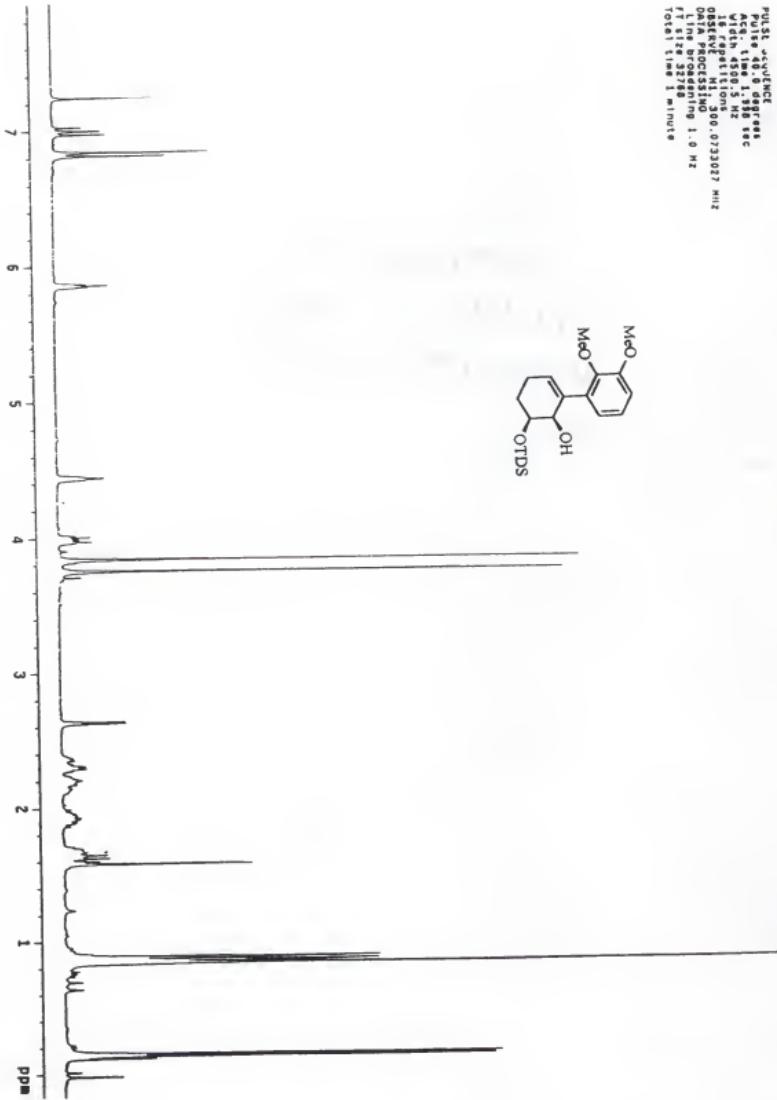


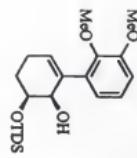
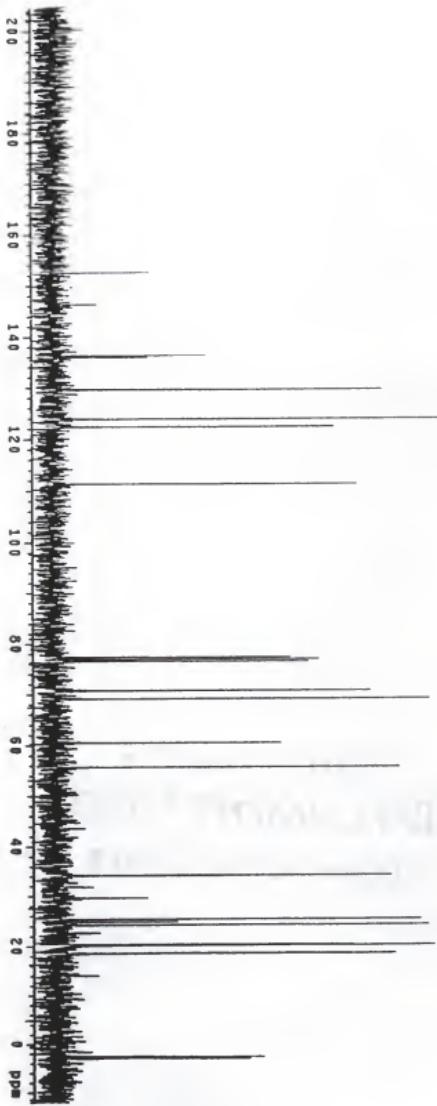
Reduced diisobutylphenyl diol

GRADIENT 75.49%  
PULSED FIELD GRADIENT 1.0  
ACQUISITION TIME 0.000  
RELAXATION DELAY 0.000  
PULSE WIDTH 5.0 microseconds  
AMBIENT TEMPERATURE  
NO. REPETITIONS 134  
DQCOIL 11.07 E  
DECIMPLER 0.75  
WALTS MODULATED ON  
DOUBLE PRECISION ACQUISITION  
DATA PROCESSING 0.5 H  
LINE BROADENING 0.5 H  
PPM 200-220  
TOTAL ACQUISITION TIME 17 minutes



PULS: 90.0 degrees  
Pulse: 1.0 sec  
Acc. time: 1.0 sec  
S: 1.0 sec  
16 repetitions  
observe: Hz, 300.0733027 MHz  
Data precision: 1.0 Hz  
Line broadening: 1.0 Hz  
Total time: 1 minute





INOVA-500 "Gemini 300"

PULSE SEQUENCE

Pulse 33.5 deg FID

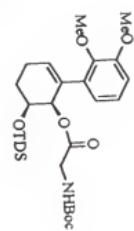
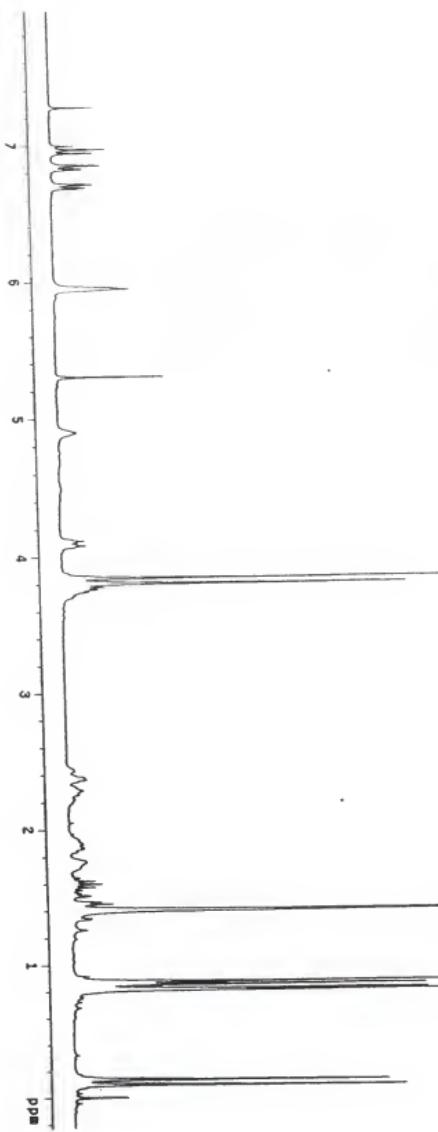
ACQ 1000 32768

DATA 1000 0.072244 MHz

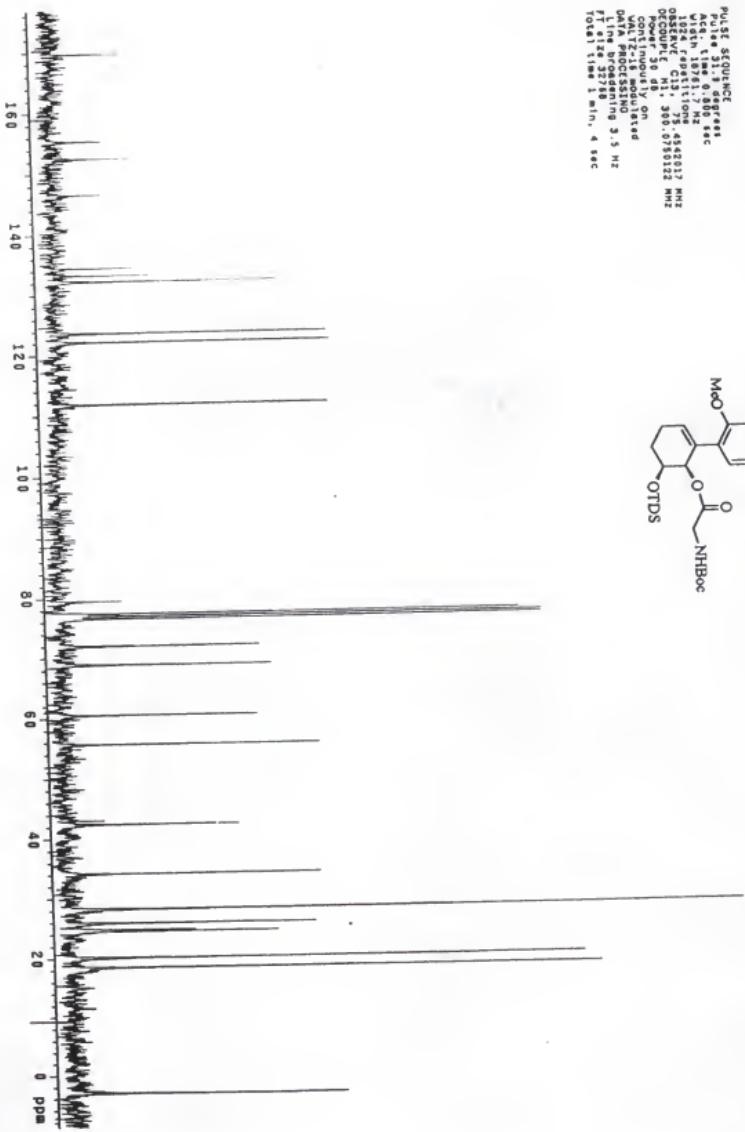
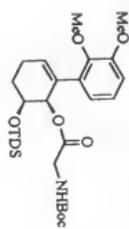
DATA PROCESSING 1.0 Hz

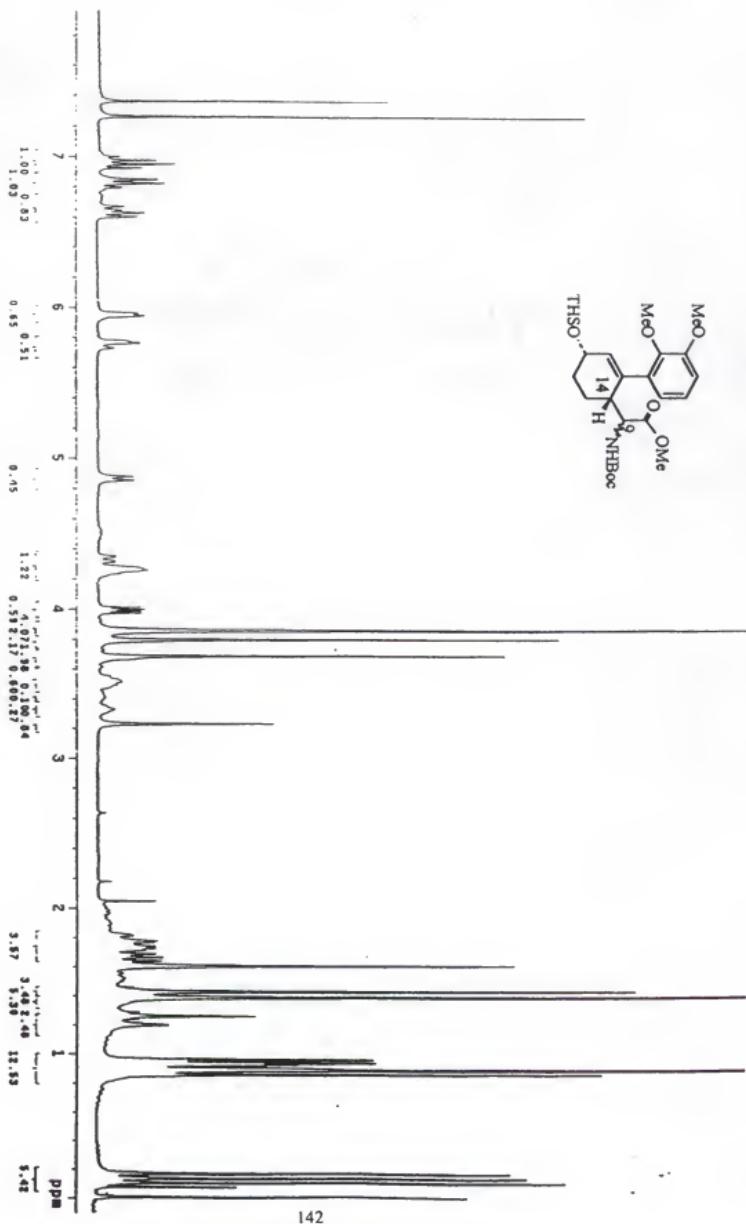
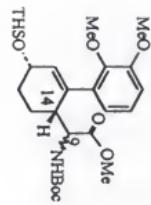
FILE SIZE 32768

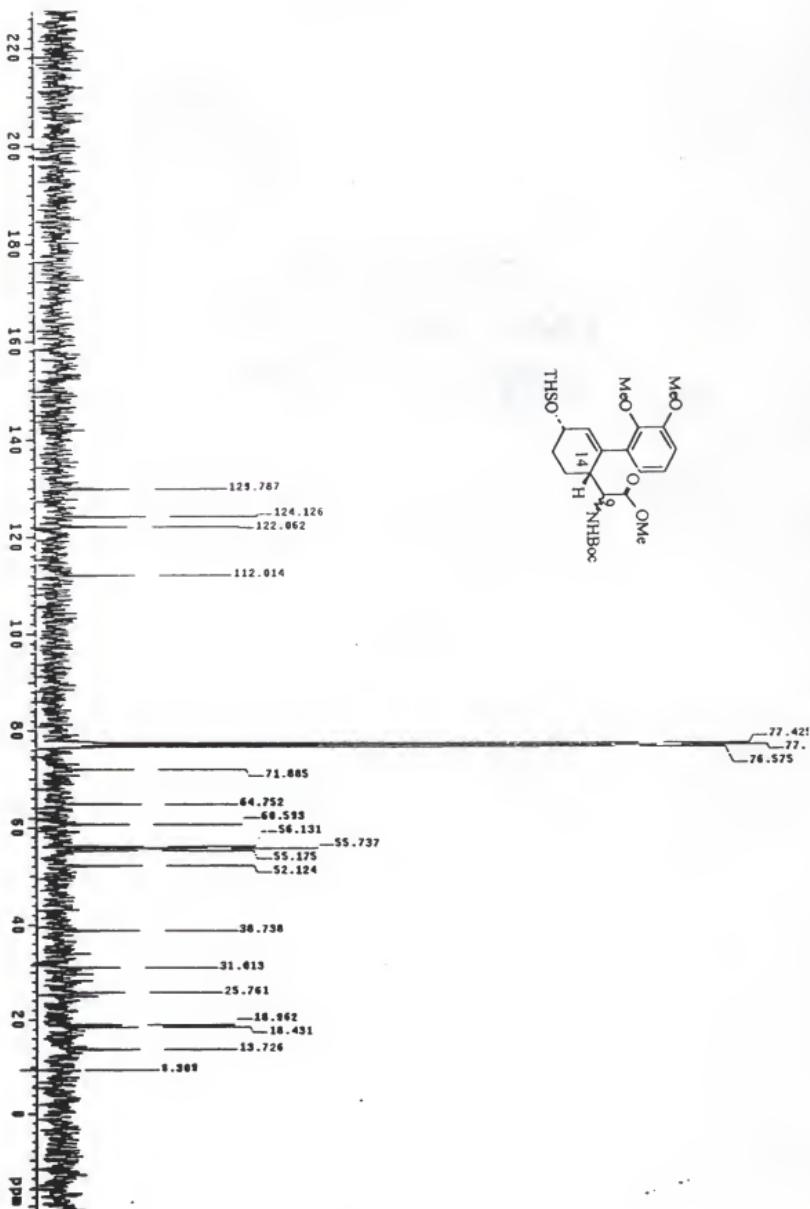
Total time 0 min. 0 sec



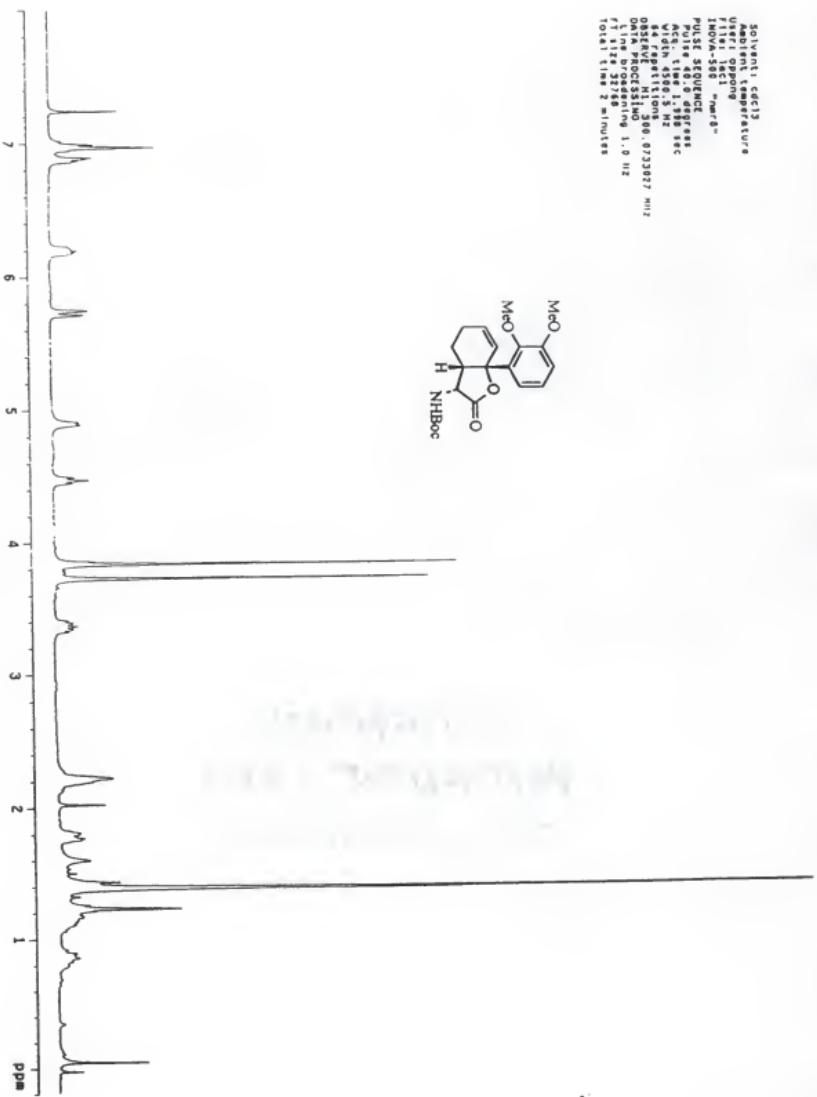
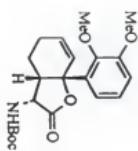
Pulse 3J-1H heteronuclear  
Acq. time 0.050 sec  
Width 18711.1 Hz  
Decoupling C13 75.454217 MHz  
Decoupler 30 dB  
Power 30 dB  
VNAZ-16 modulated  
Data processing 0.5 Hz  
F-LINE broadening 3.5 Hz  
Total time 1 min, 4 sec

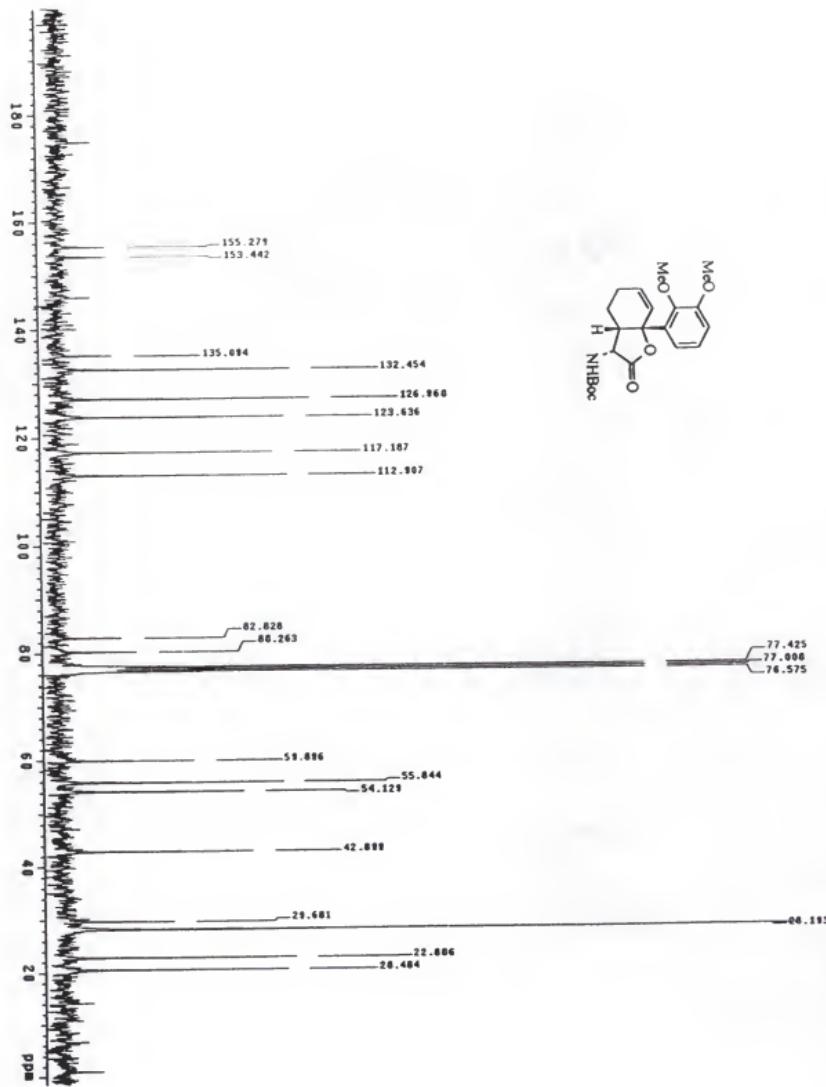




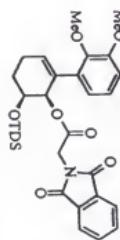
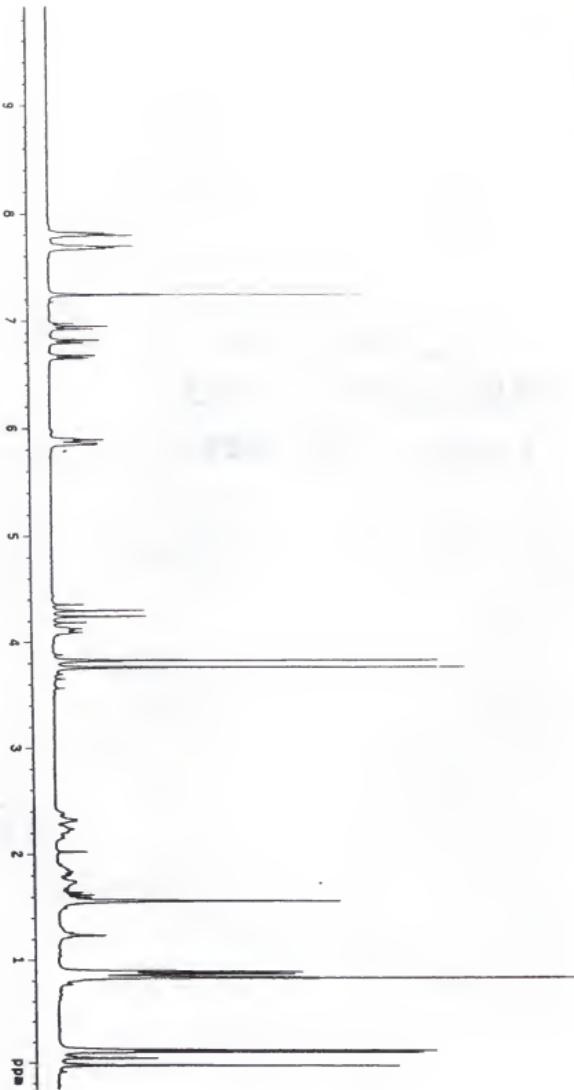


startdelay, 1.000000  
waitforresponse, 0.000000  
file, "test", "new", 0  
INNOVA-5600  
PULSE SEQUENCE  
2D  
Pulse, 4.000000, 1.000000, 0.000000  
width, 4199.5, Hz  
64, FID1, 0.0733627, 0.012  
0.000000, 0.000000, 0.000000  
Line processing, 1, 0, 12  
line size, 256  
Total, 2, 1.000000

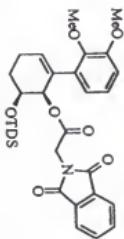
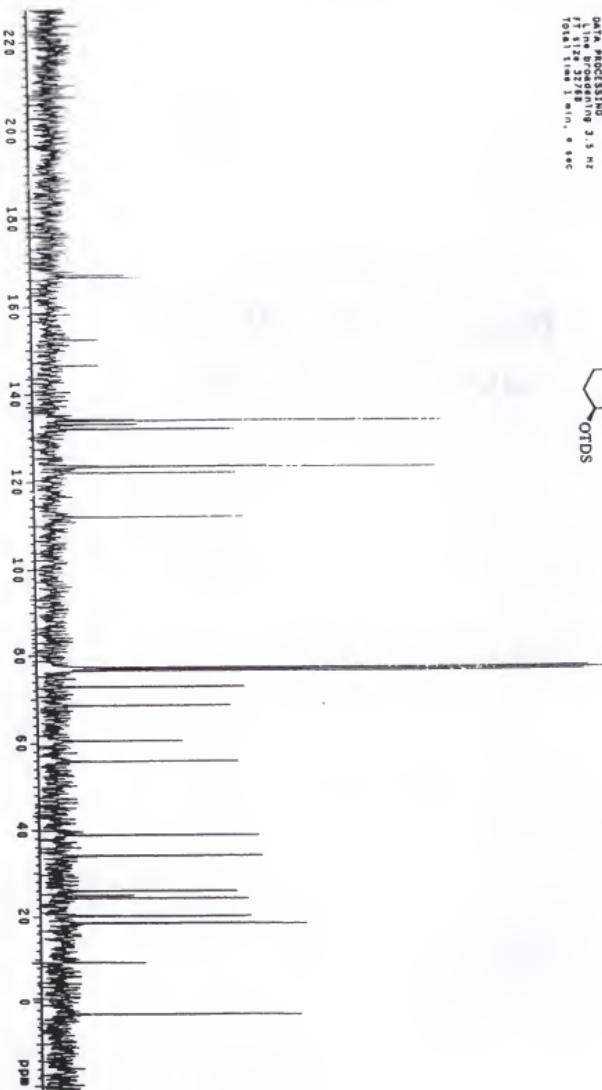




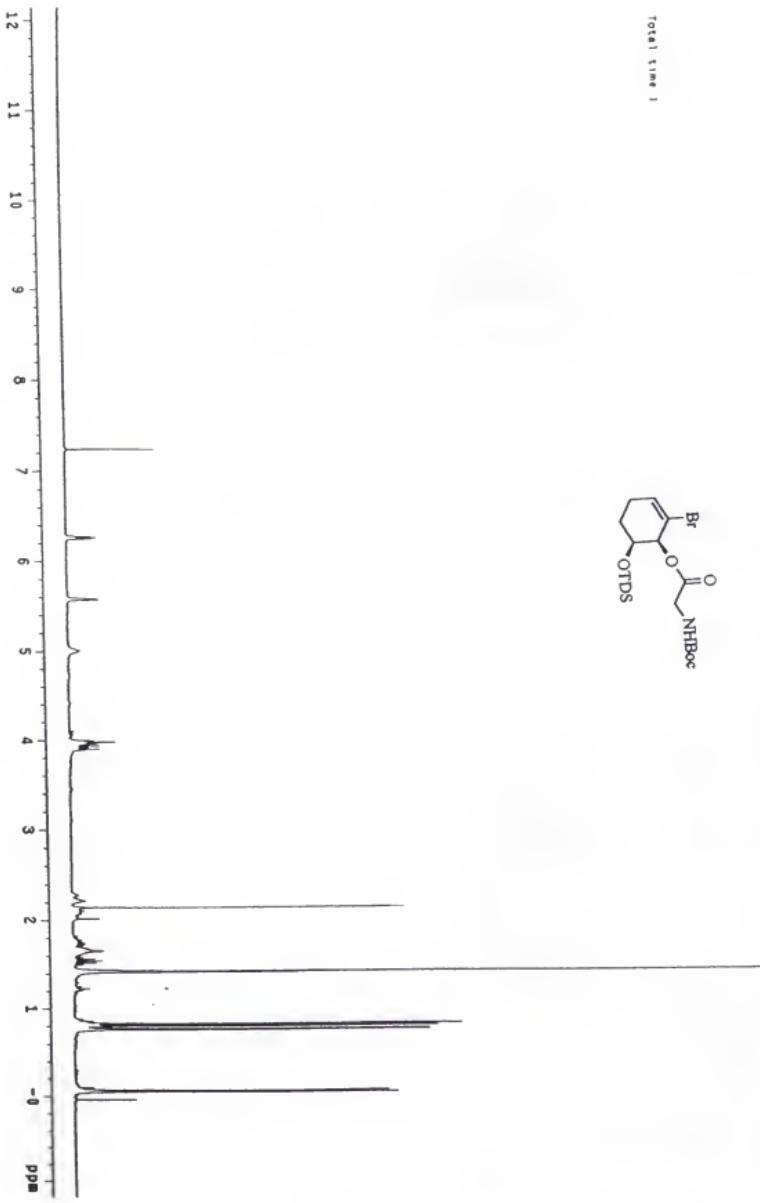
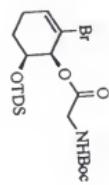
Solvent: CDCl<sub>3</sub>  
ambient temperature  
TELECHEM 300 "General"  
TOMOVA 500 "General"  
PULSE SEQUENCE: 90°-180°-180°  
Pulse 135 deg 4.0 sec  
Width 1.0 sec  
4 repetitions  
DOSAGE: 100.000001 MHz  
Line broadening: 1.0 Hz  
RT line 327.0  
Total time 0 min., 4 sec

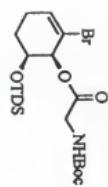
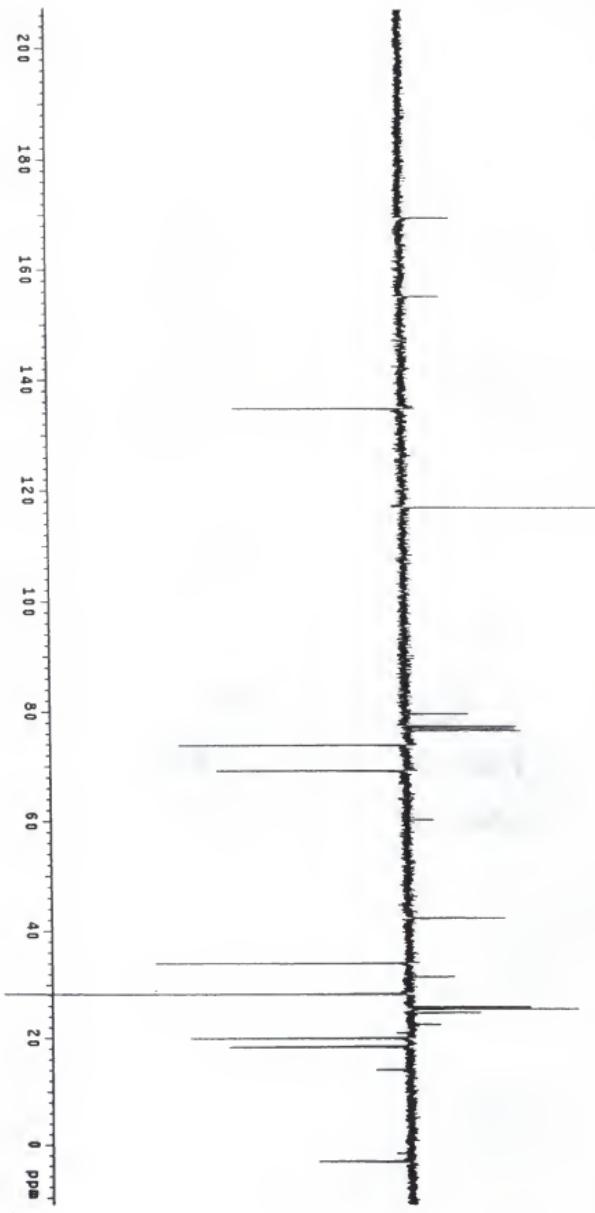


ambient temperature  
User opening  
Initial-RDFT, "seen in 1900"  
Pulse 90°, 100 Hz  
Pulse 31°, 100 Hz  
Acq time 0.300 sec  
Vibrat separation 100 sec  
Observe C13: 75.65±20.05 MHz  
Decouple H1: 300.77±0.12 MHz  
Chemically unlabelled  
Valence modulated  
Data processing 3.5 Hz  
FID 32768  
Total time 1 min. 0 sec



Total time 1





Standard NMR parameters

Pulse sequence: 82us

Solvent: CDCl<sub>3</sub>

Solvent temperature = "quintin30"

OTELNLSQ08

PULSE SEQUENCE

Pulse 32.7 degres

Ach. time 3.118 sec

Wait 10.000 sec

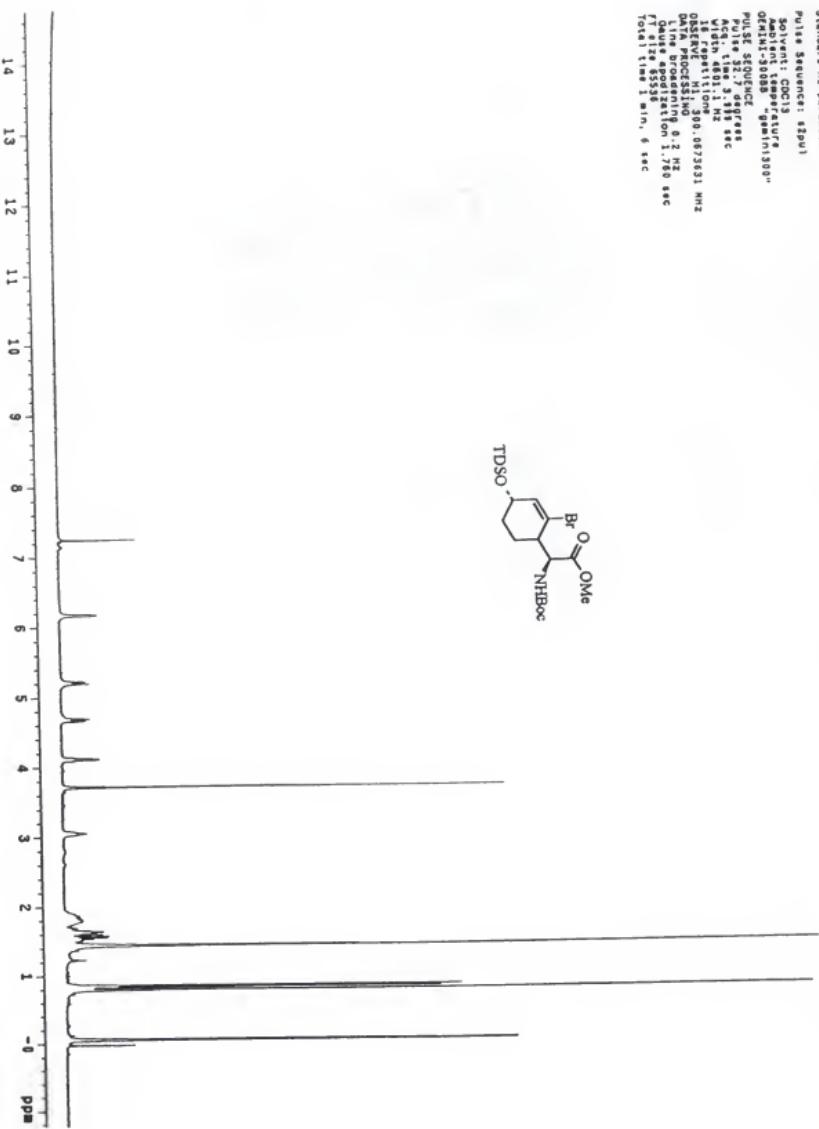
Observe 10.000.000.000.000.000 Hz

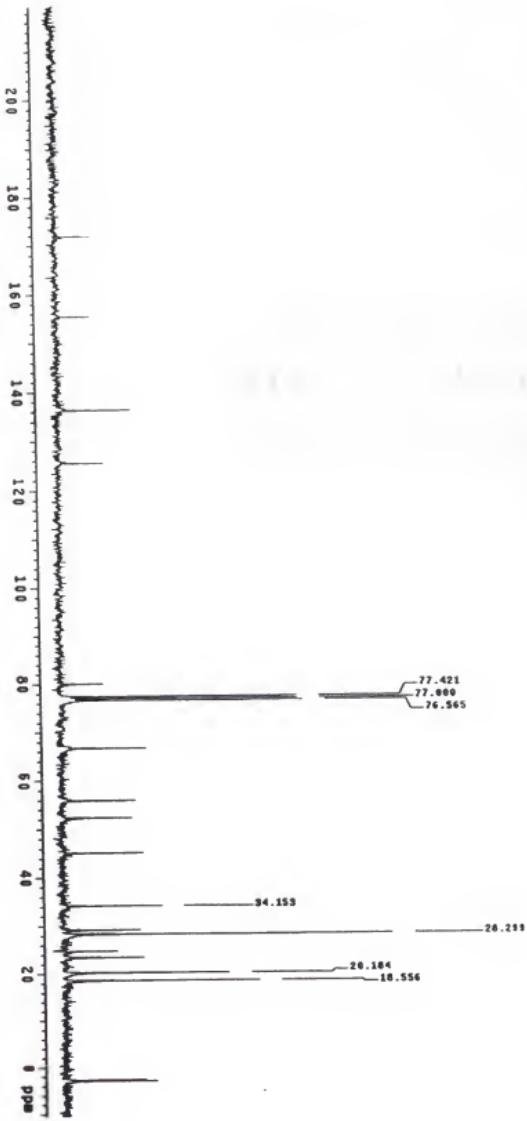
Data Proc 32700.02 MHz

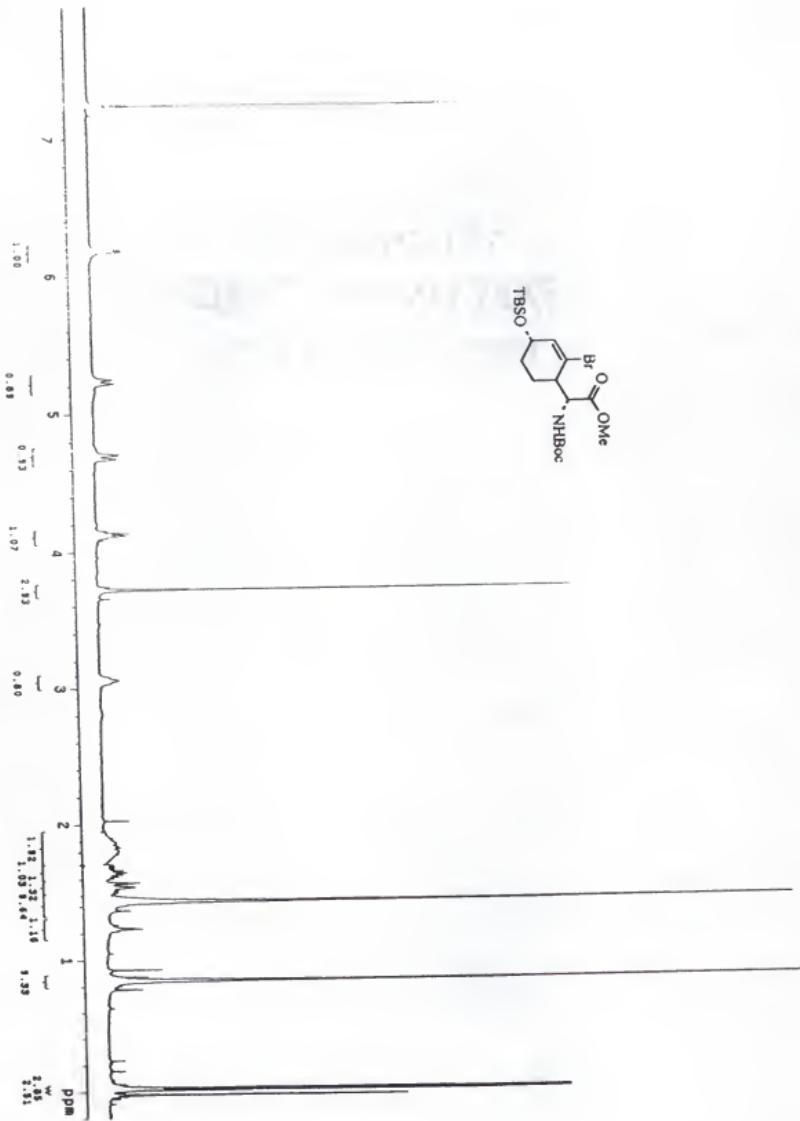
Qline broadening 0.2 Hz

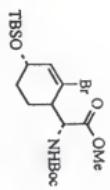
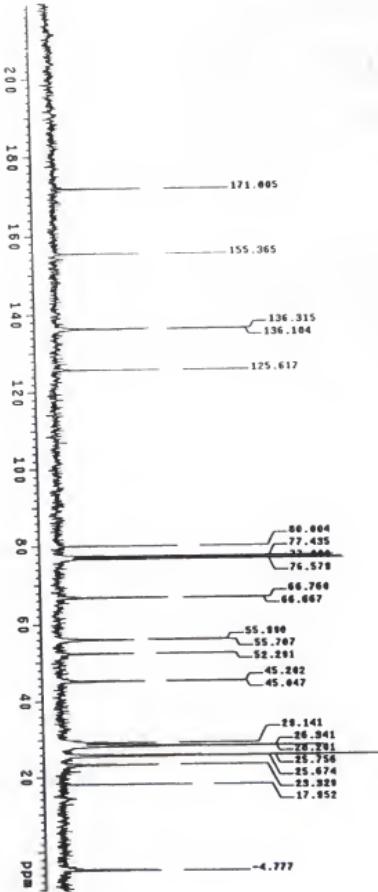
Qline broadening 1.760 sec

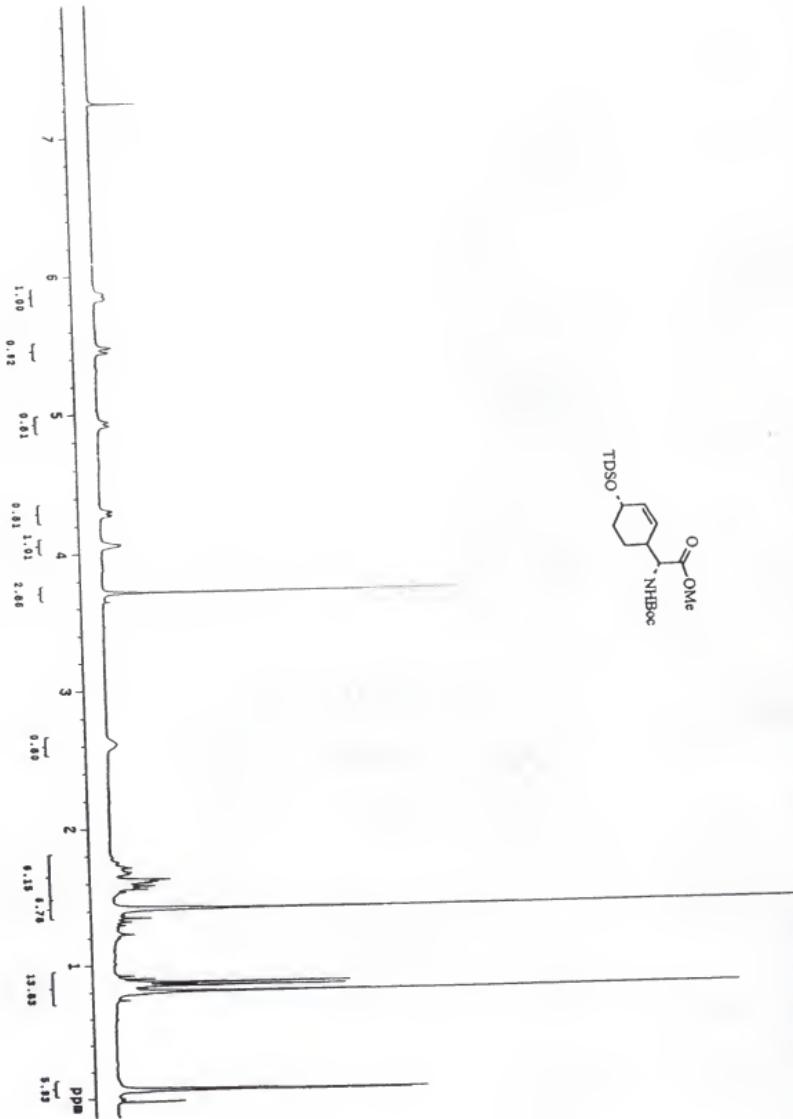
Total time 1 min. 6 sec

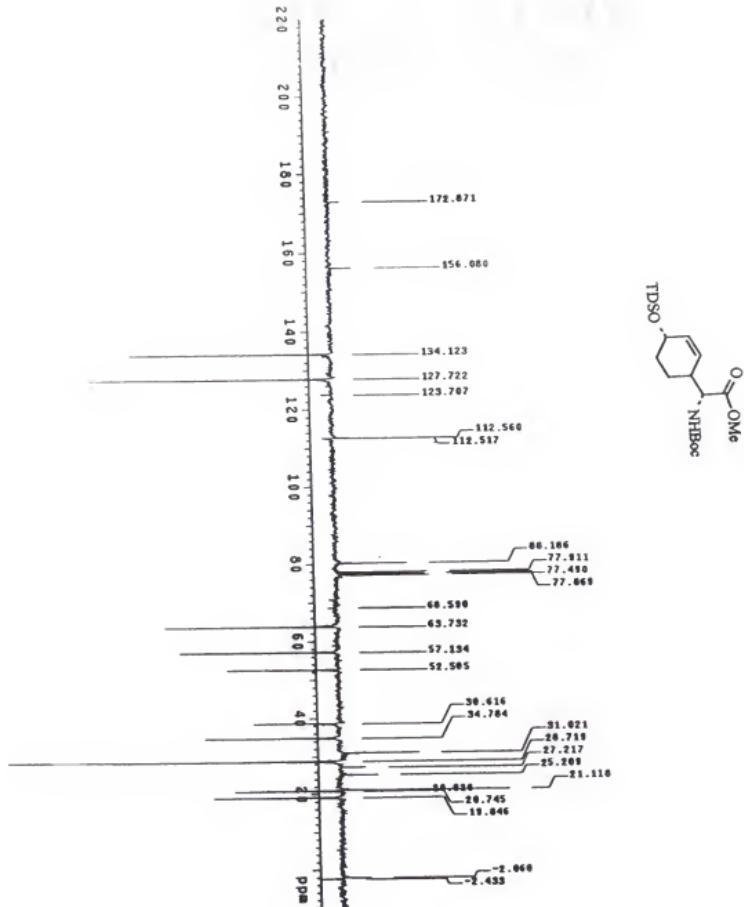




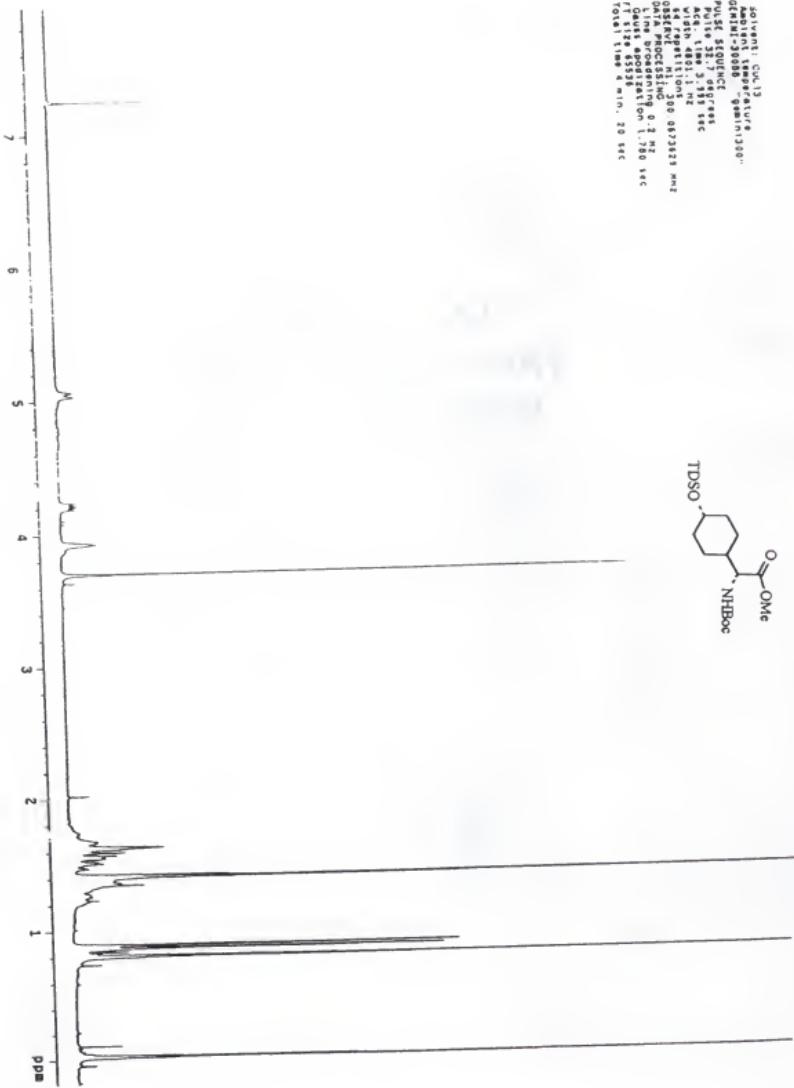
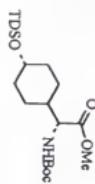


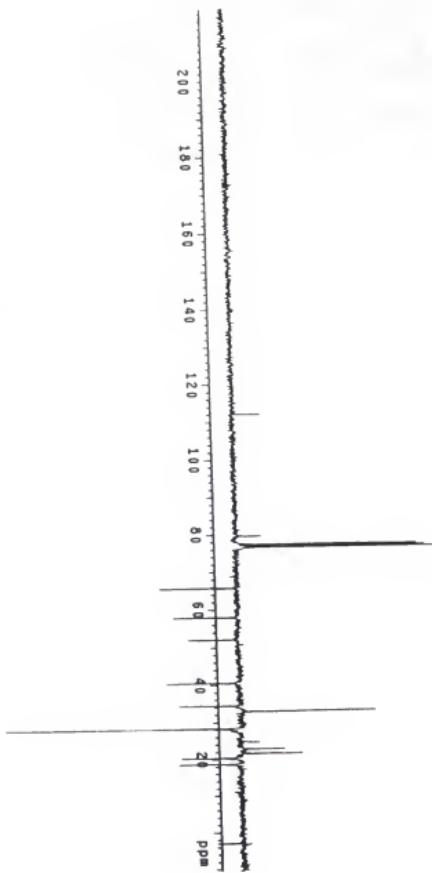
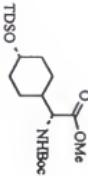




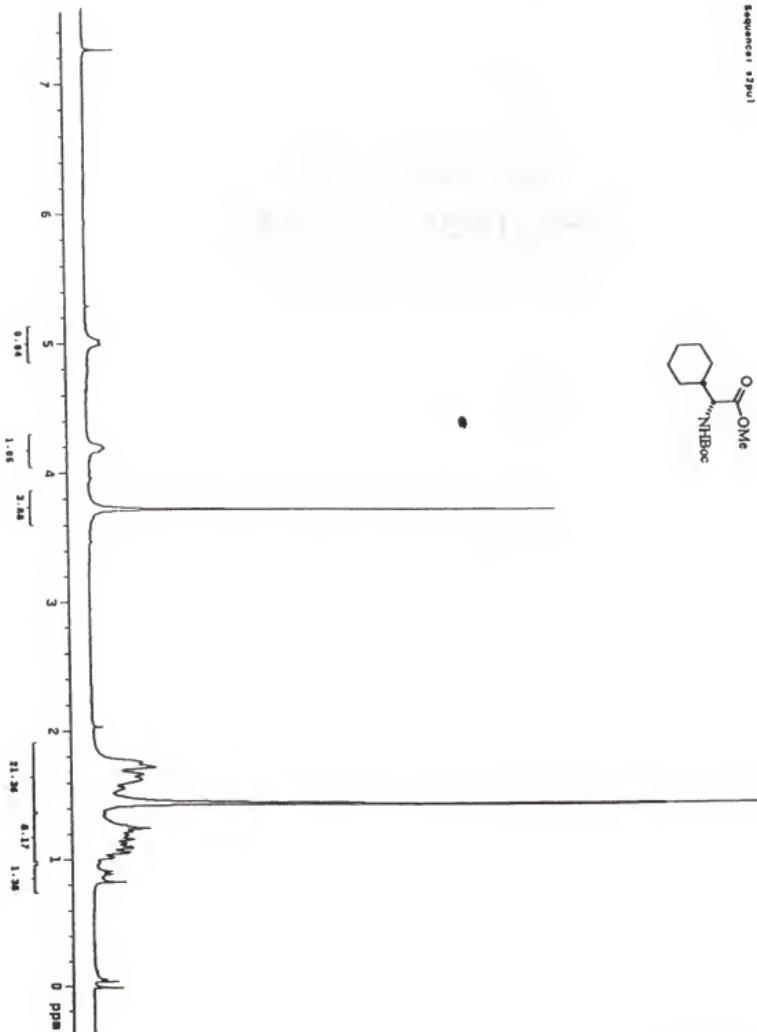


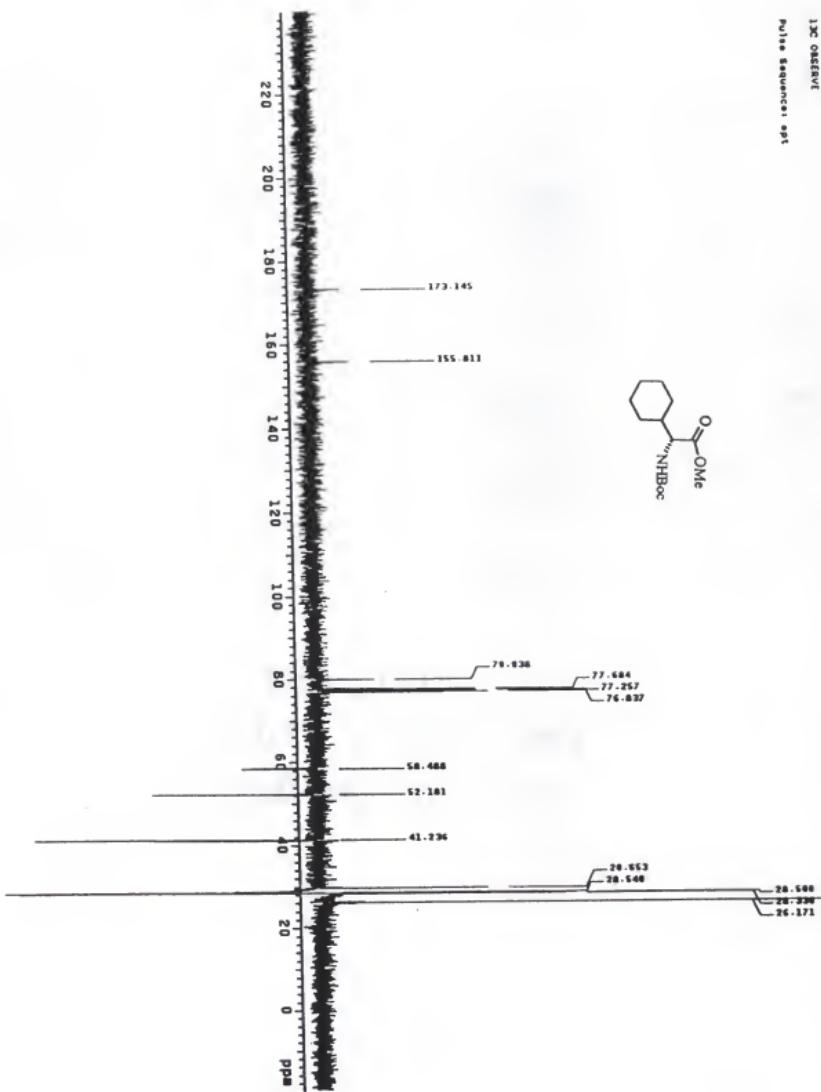
Solvent: CDCl<sub>3</sub>  
Acetone-D<sub>6</sub> mixture 1:9  
OEMH-<sup>13</sup>C NMR  
Pulse sequence: CPMAS  
Pulse time: 3.145 sec  
Acq. time: 3.145 sec  
Width: 1 Hz  
Sweep width: 100 Hz  
Data processing: 0.073423 min  
Line broadening: 1.2 Hz  
Line width: 1.780 sec  
Printed: 4/26/96 10:20 AM  
Total time: 4 min. 20 sec



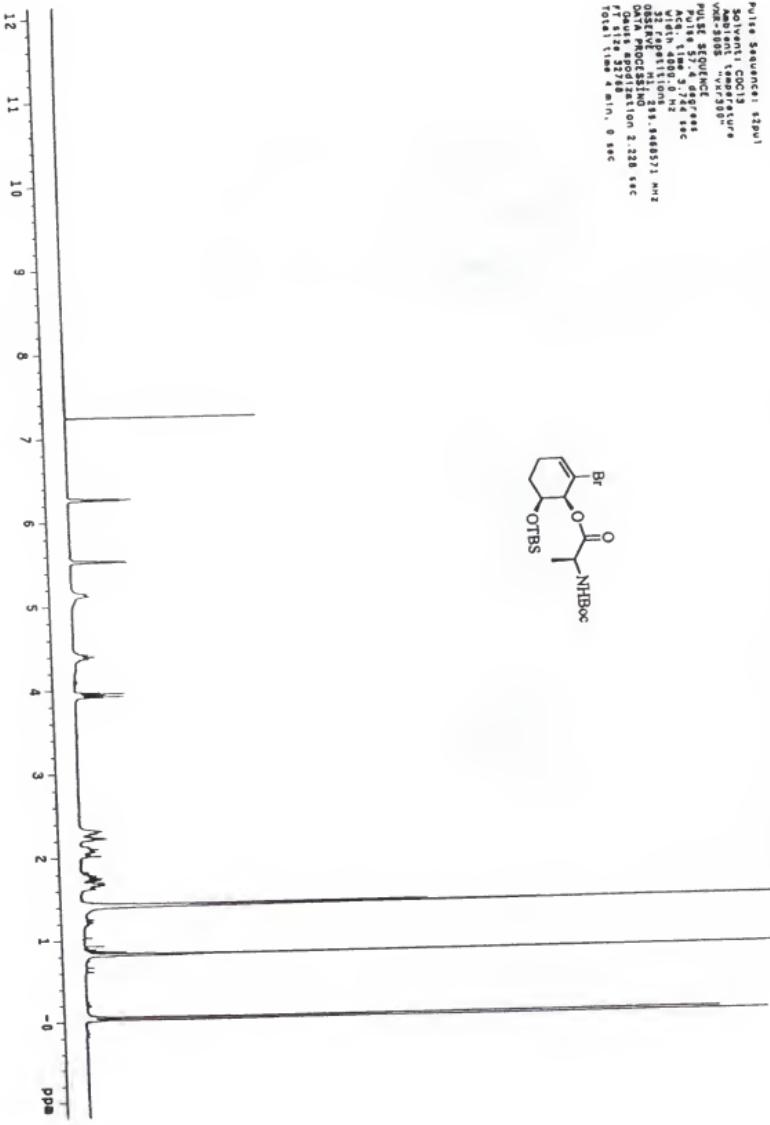
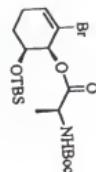


1H NMR IN DMSO-D<sub>6</sub>  
Pulse Sequence: 9.7μs





Pulse Sequence: 90°pul  
Solvent: CDCl<sub>3</sub> / Acetone  
Volume: "var100"  
Pulse: 90°, dephas  
Pulse time: 3.74 sec  
Acq. time: 1.0 sec  
Vdd: 100.0 Hz  
Observe: 131.448871 MHz  
Data processing: 2.228 sec  
Quis: 122.0 Hz  
Polarization: 4 min, 0 sec



Pulse Sequence: esp1

Acquisition: 1D, 13C

Number of scans: 2000

Wavercav: 360 "Wavercav:360"

Pulse sequence: esp1

1st pulse: 180.0 degrees

2nd pulse: 135.0 degrees

3rd pulse: 135.0 degrees

Width: 8851.4 Hz

With 3120 repetitions

OBSERVE: CH1

POWER: 1.0

Phase: 13 deg

On our 1H acquisition

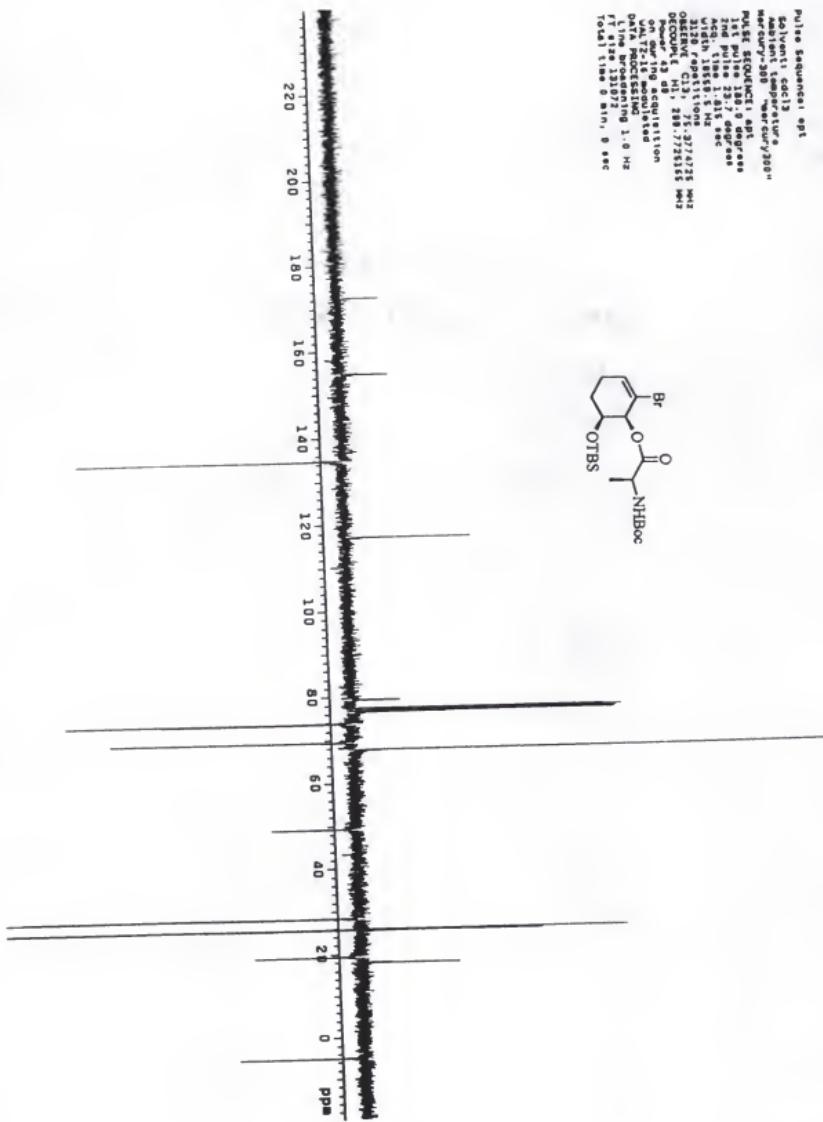
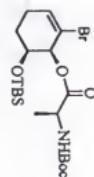
1D, 13C

DATA PROCESSING:

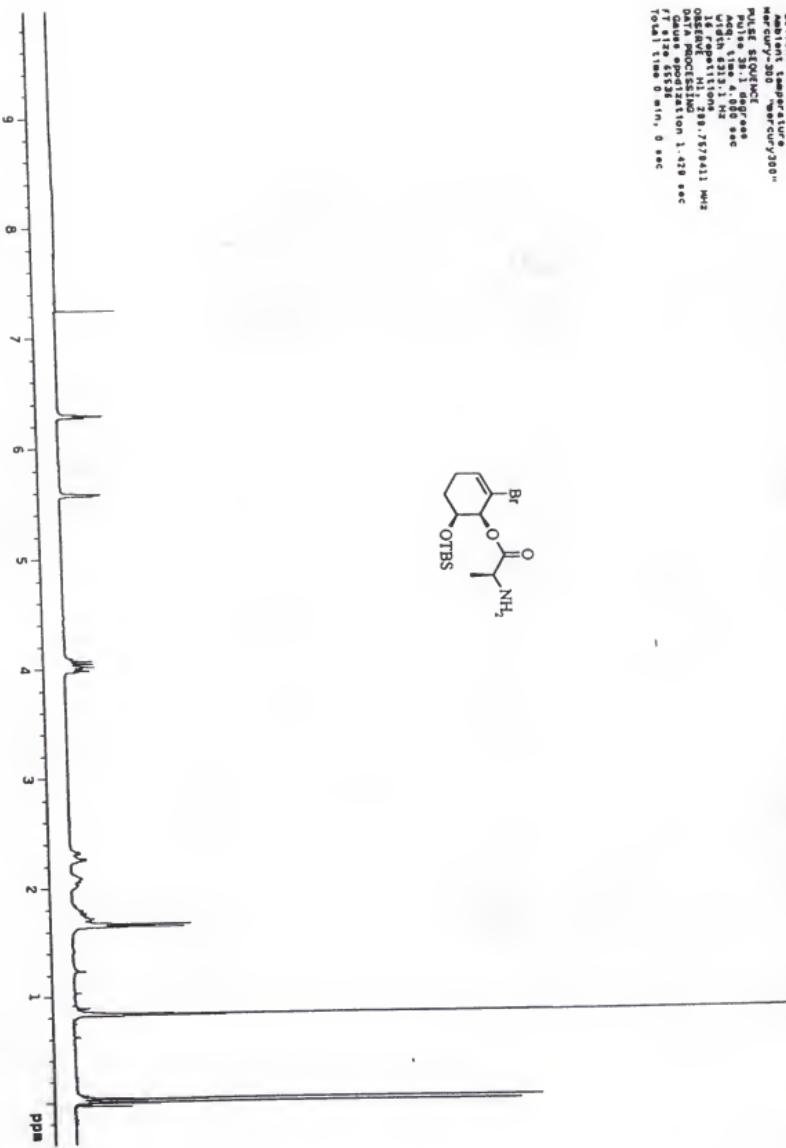
Line broadening: 1.0 Hz

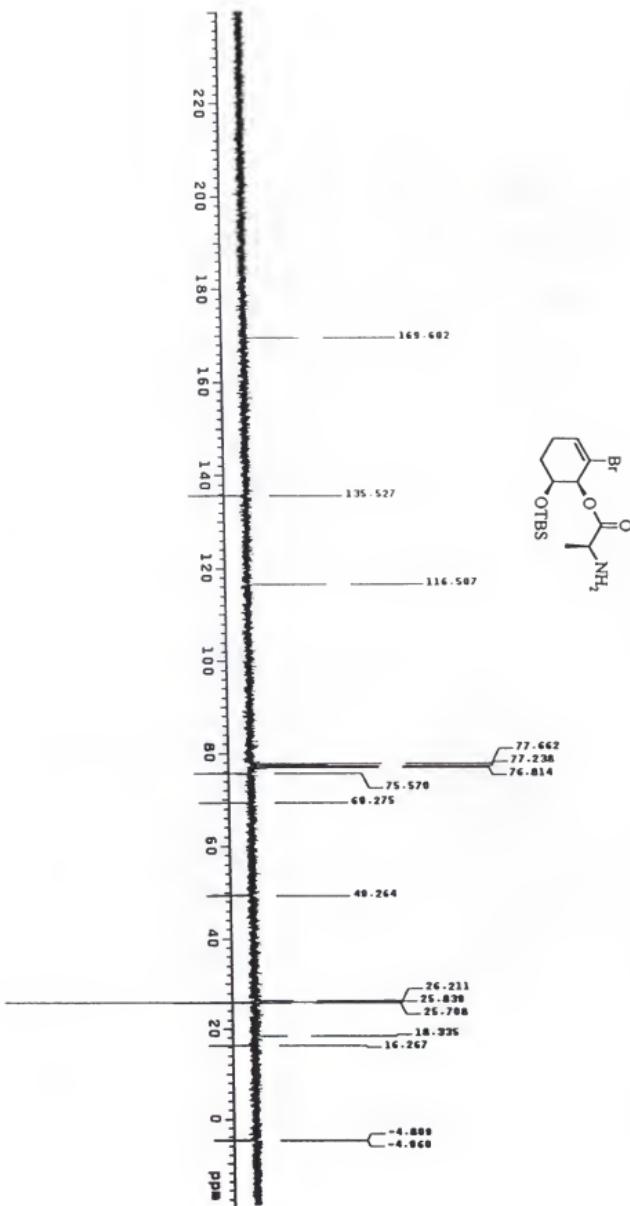
FT size: 131072

Total time: 0 min, 0 sec

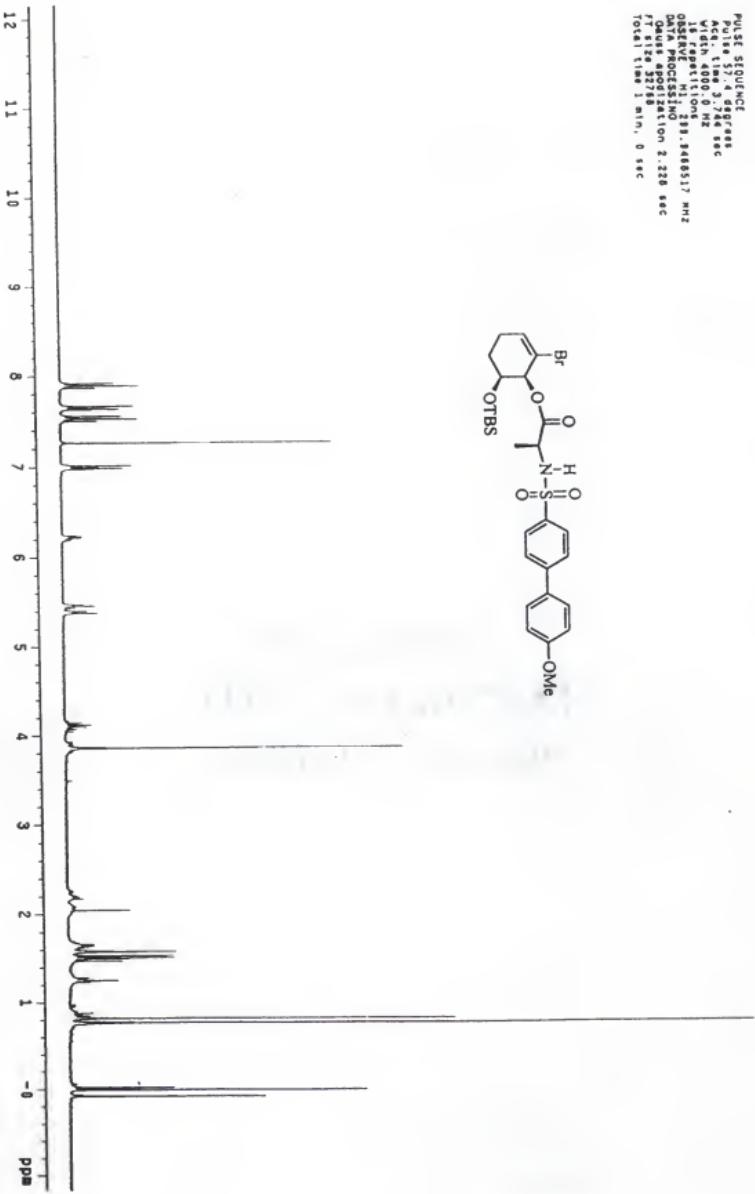
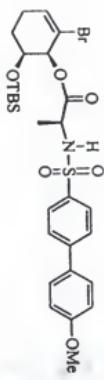


Solvent: CDCl<sub>3</sub> / Acetone-d<sub>6</sub>  
ambient temp  
Mercury 300  
new capillary  
Wedge  
Pulse 90 degrees  
Acq time 4.00 sec  
Width 621.1 Hz  
Ave 1  
Sweep width 7500 Hz  
Data processing: 1.429 sec  
Gauss apodization: 1.429 sec  
FID size 65536 points  
Total time 6 min, 0 sec

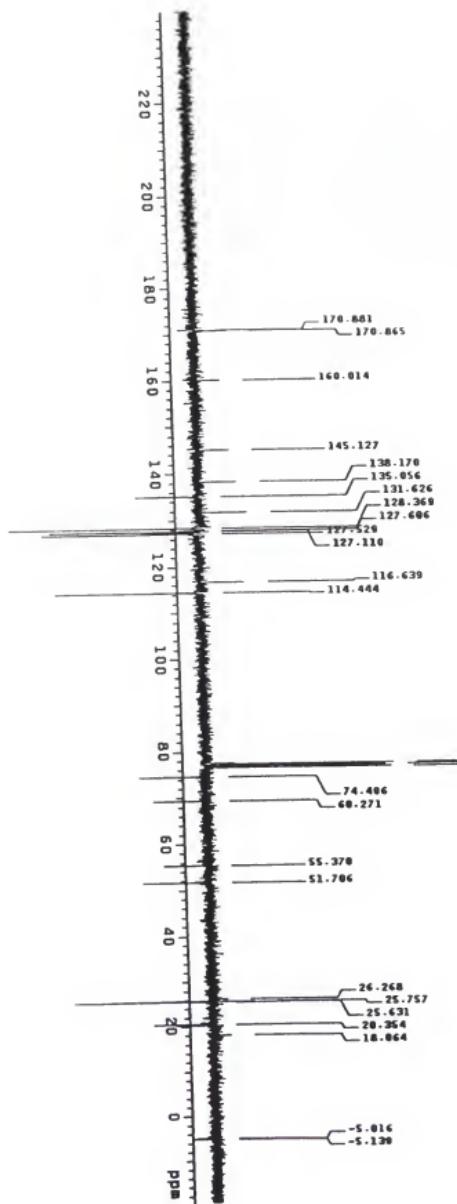
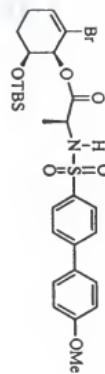




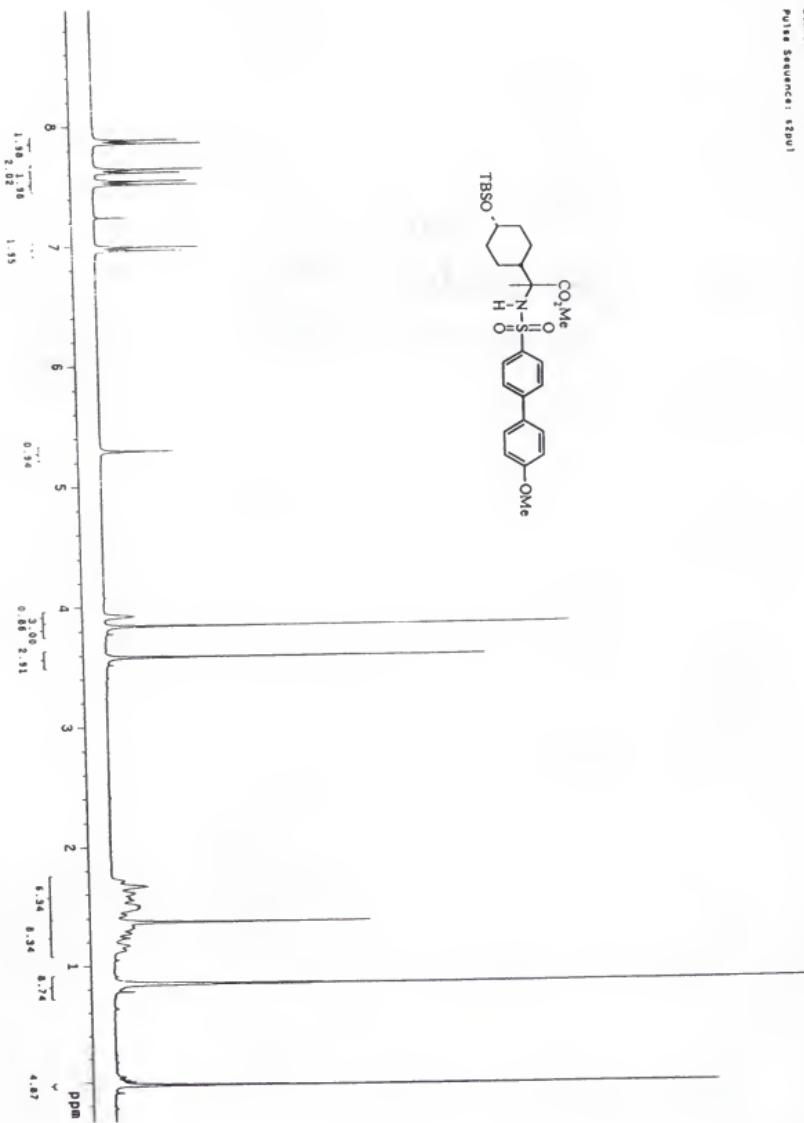
Pulse 53.0 degrees  
Pulse time 3.744 sec  
Acq. time 4000.0 msec  
Width 4000.0 Hz  
112 repetitions 18.446517 MHz  
Data processing 1.446517 Hz  
Quadrupole decoupling 2.228 sec  
FT size 32768  
Total time 1 min, 0 sec



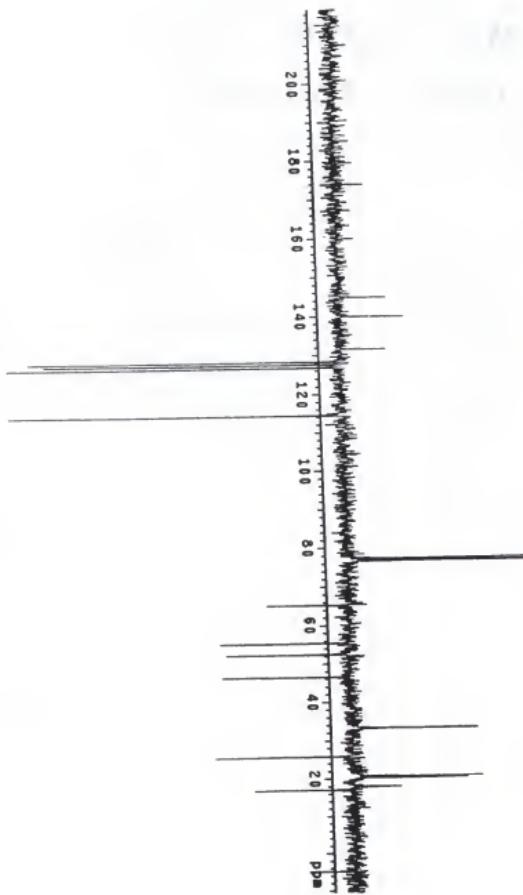
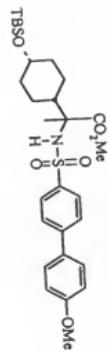
Pulse Sequence: ap1



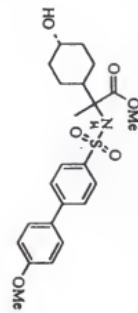
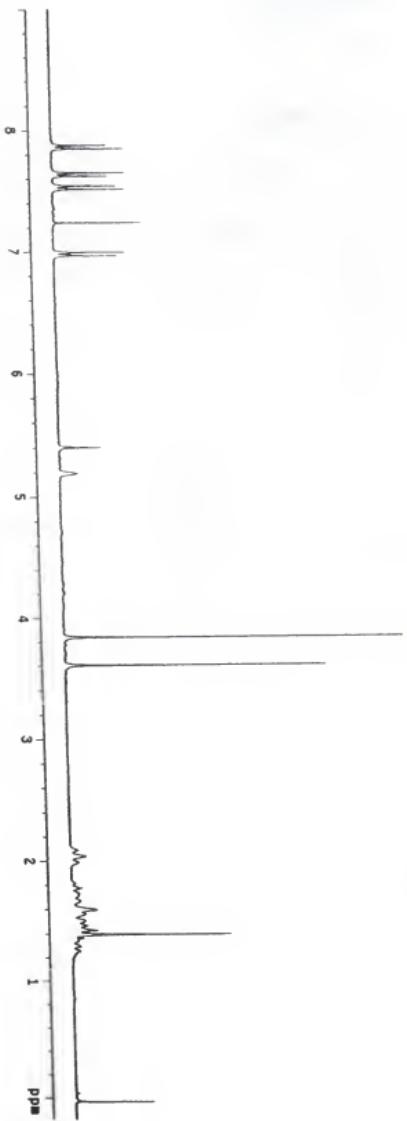
Standard <sup>1</sup>H parameters  
Pulse Sequence: zgpu1



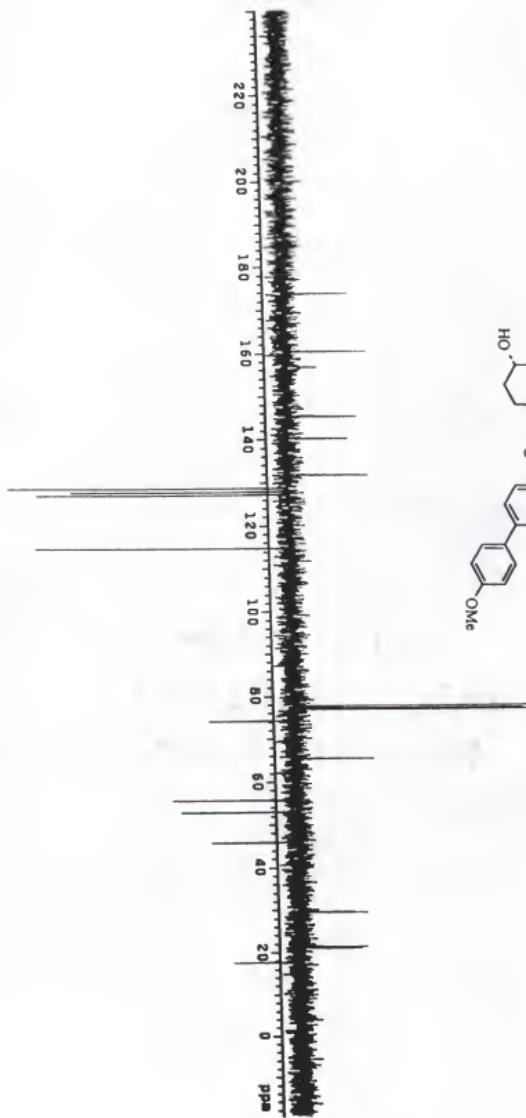
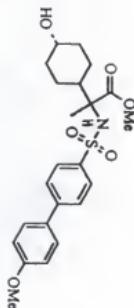
PULSING: 90° after  
90° pulse 25.0 degress  
90° pulse 25.0 degrec  
Accq. time 0.4 sec  
Width 1.4 sec  
DETECTOR: C13, 482005 MHz  
DECOUPLER: H1, 366.068364 MHz  
POWER: 100% calculation  
WAVETE: 8 modulated  
DATA PROCESSING:  
LINE BROADENING 3.5 Hz  
FT LINE BROADENING 3.5 Hz  
TOTAL TIME 16 min, 33 sec



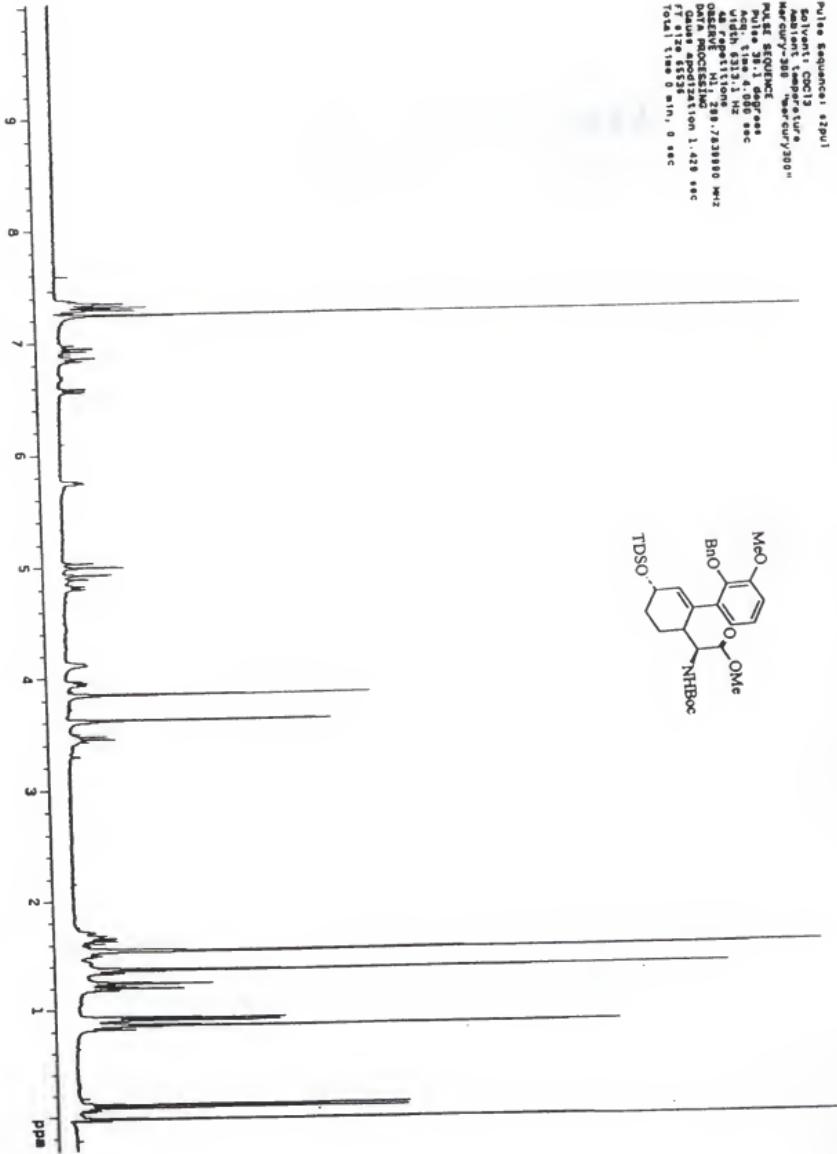
Solvent:  $\text{CDCl}_3$   
Ambient temperature  
Varian 300S - WET300  
Pulse sequence: 90°  
Pulse time: 1.00 sec  
Acq. time: 0.0 sec  
With 1600 Hz  
18 repetitions  
Obsv. freq.: 300.144558 MHz  
DQF-COSY  
Dw: 10.0 sec  
FID size: 32768  
Total time: 1 min., 0 sec

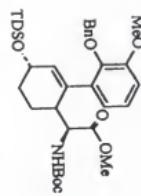
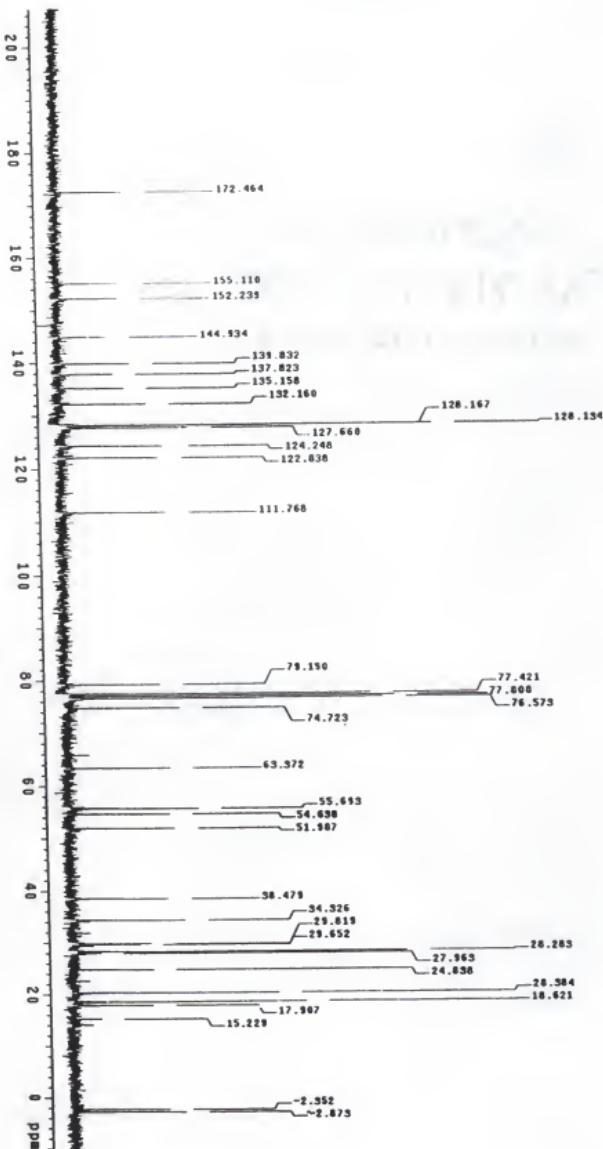


Pulse 180.0 degrees  
Time 22.7 degrees  
Acc. time 1.65 sec  
Width 1.6881 Hz  
Decoupler 70.0 Hz  
Decouple C13 70.5, 27.0148 Hz<sup>13</sup>C  
Power 42 dB  
Line width 1.0 Hz  
Data processed  
Line broadening 1.0 Hz  
Total time 16 min, 15 sec



Pulse sequence: 62pu1  
Solvent: CDCl<sub>3</sub>  
ambient temperature  
Marconi-300 "Mercury 200"  
PULSE SEQUENCE:  
Pulse 30.1 degrees  
Acq. time 4.00 sec  
Value 1024  
Data points 1024  
Observe H1, TMS, 2838880 Hz  
Data processed 1.428 sec  
Data acquisition 1.428 sec  
Total time 0 min, 0 sec





STANDARD <sup>1</sup>H PARAMETERS

Pulse Sequence: 62pu1

Solvent: CDCl<sub>3</sub>

Ambient Temperature

VNA=0.03

PULSE SEQUENCE

Pulse 51.7°, 3.74 sec

Width 400.0 Hz

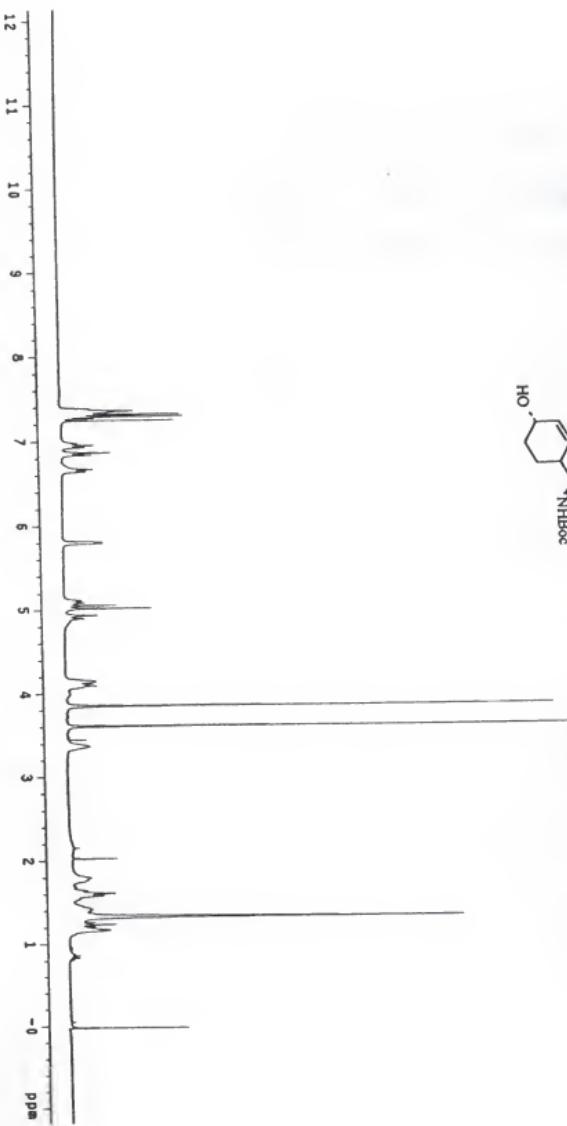
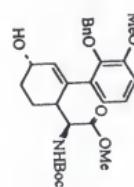
1H Resolution 1.448573 MHz

OBSC Frequency 31.448573 MHz

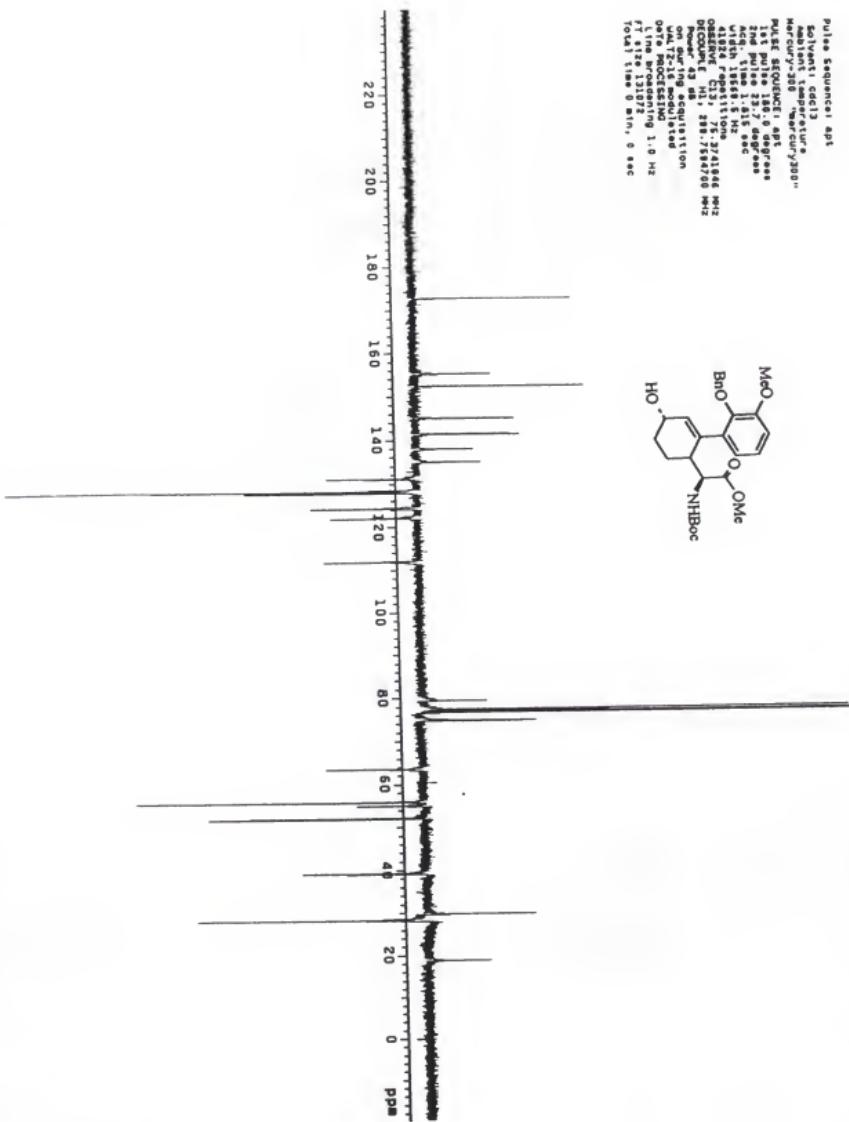
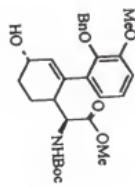
Quies Acquisition 2.228 sec

FT Size 22780

Total Time 1 min., 0 sec



Pulse Sequence: ap1  
Solvent: CDCl<sub>3</sub>  
ambient temperature  
Marcury-300 "Marcury300"  
PULSE SEQUENCE: ap1  
135° pulse 135.7° degrees  
135° pulse 135.7° degrees  
Acq Time: 1.015 sec  
Width: 1368.5 Hz  
A1324 Protonation  
Decoupling: H1, 281.754846 Hz  
Power: 43 dB  
on during acquisition  
on during decoupling  
Data Processing: 1 sec  
Line broadening: 1.0 Hz  
FID size: 131072  
Total time: 0 min, 0 sec



STANDARD <sup>1</sup>H PARAMETERS

Pulse Sequence: tdpf

Solvent: CDCl<sub>3</sub> at room temperature

Varian 300S "widebore"

Pulse 7.4 degrees

Pulse delay 1 sec

Acq. time: 1.4 sec

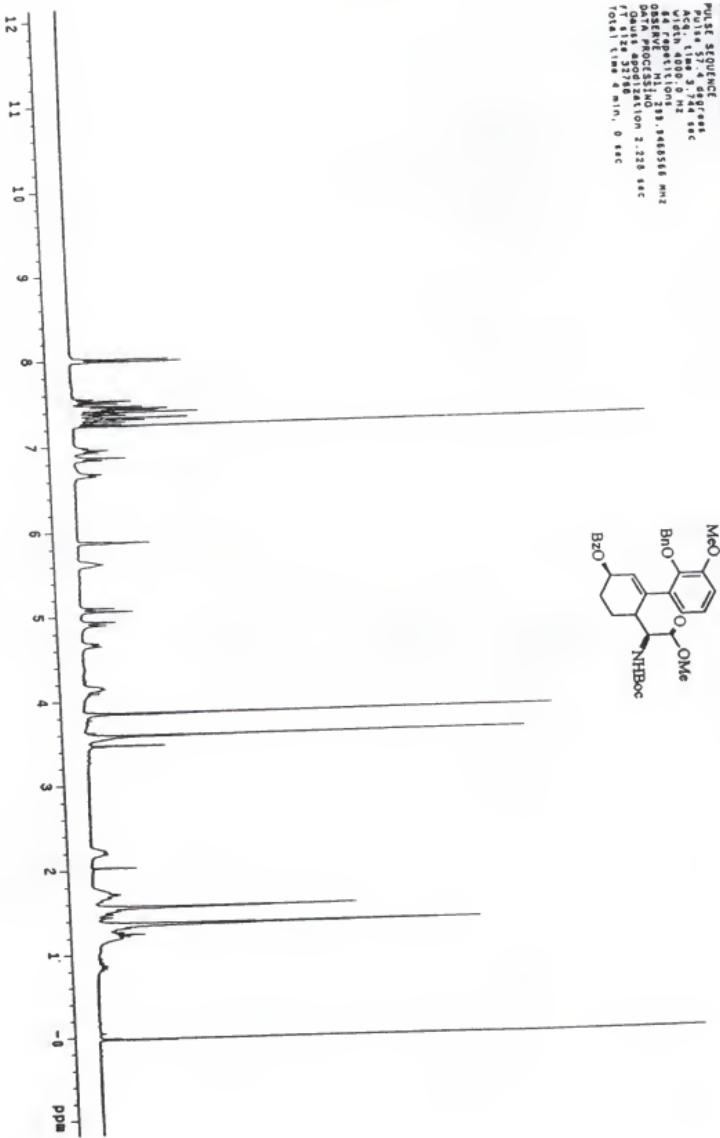
Water Suppression: 100%

Observe: <sup>1</sup>H, 235.448566 MHz

Data processing: 2.128 sec

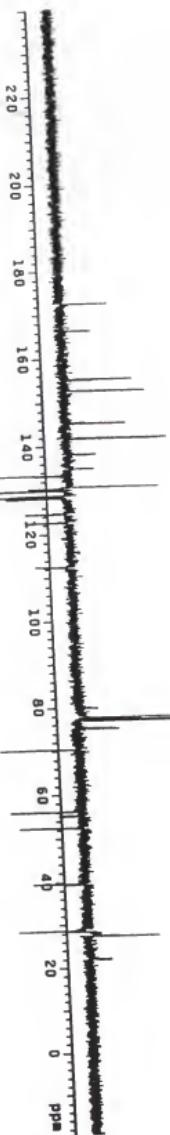
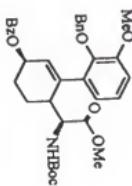
Quits: 2748 sec

Total time: 4 min, 0 sec

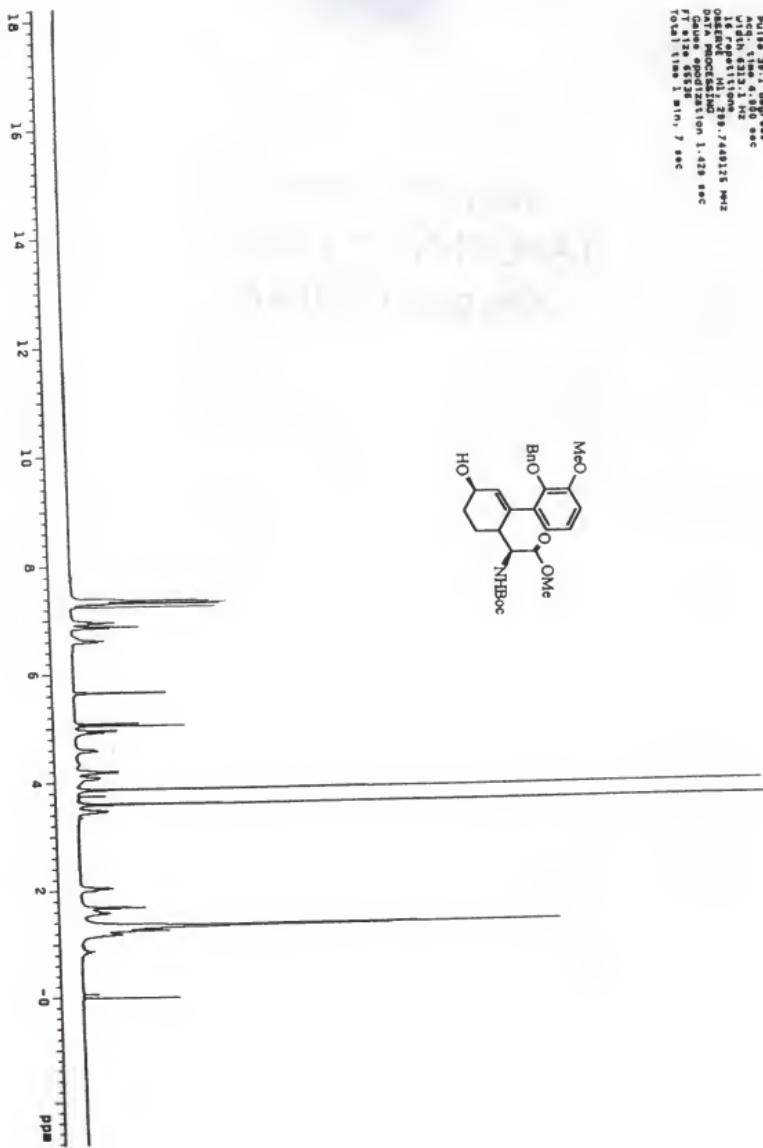


13C OBSERVE

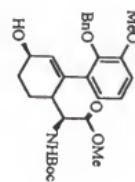
Pulse sequence: opt  
Solvent: CDCl<sub>3</sub> / TMS  
Polarization: "Mercury-300"  
Pulse sequence: opt  
1st pulse 10.0 degrees  
2nd pulse 20.0 degrees  
Acq time: 1.0 sec  
EISS repetitions: 1024  
Observe: C13, 140-240 ppm  
Decouple: 13C, 140-240 ppm  
on during acquisition  
WID: 7.5-16 ms/1024  
DTR: 1000 Hz  
FID time: 33.077 sec  
Total time: 0 min, 0 sec



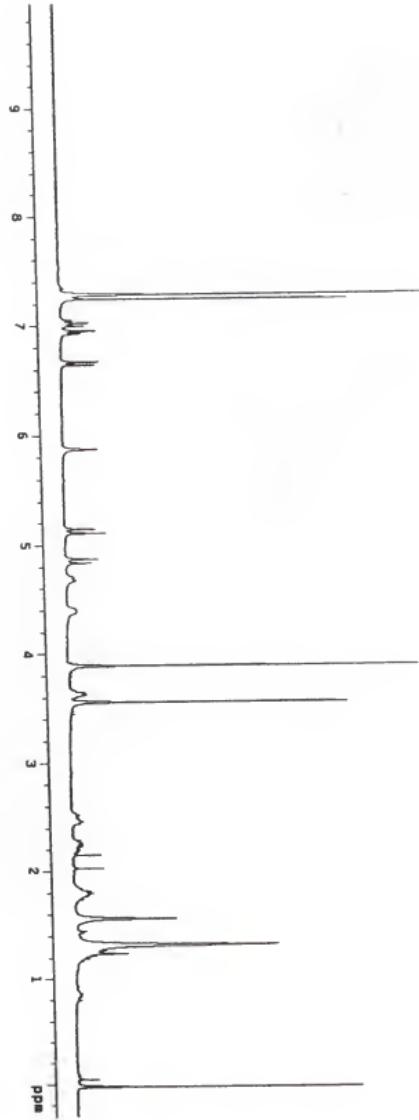
temp= 25.0 ° / 298.1 K  
magn= 300 Hz / varifreq3001  
pulse sequence  
pulse 180.1 degrees  
acq. time 4.00 sec  
with 32321 Hz  
obsv. time 299.7440125 MHz  
data points 2048  
Gauss apodization 1.42 sec  
FID size 8192, 7 sec  
Total time 1 min, 7 sec



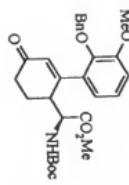
453 pulses, new 90° degree  
7200 points, 1 sec. dec.  
width 16681.5 Hz  
812 repetitions  
OBSERVE: C13, 270-244238 Hz  
PROBE: 49 mm  
on during acquisition  
JUL-721K probe selected  
DETECTOR: PMT  
Pulse width setting 1.0 Hz  
RT: 6120.218972  
Total time 34 min., 30 sec

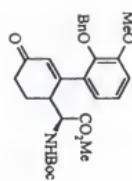
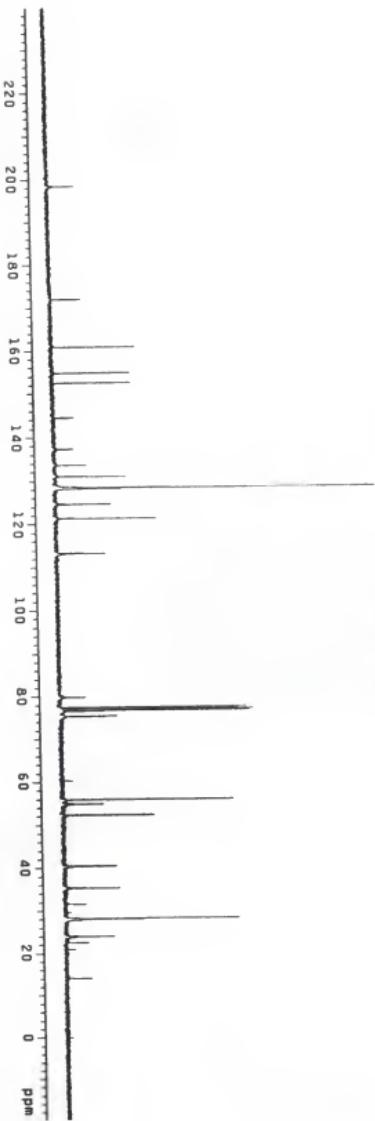


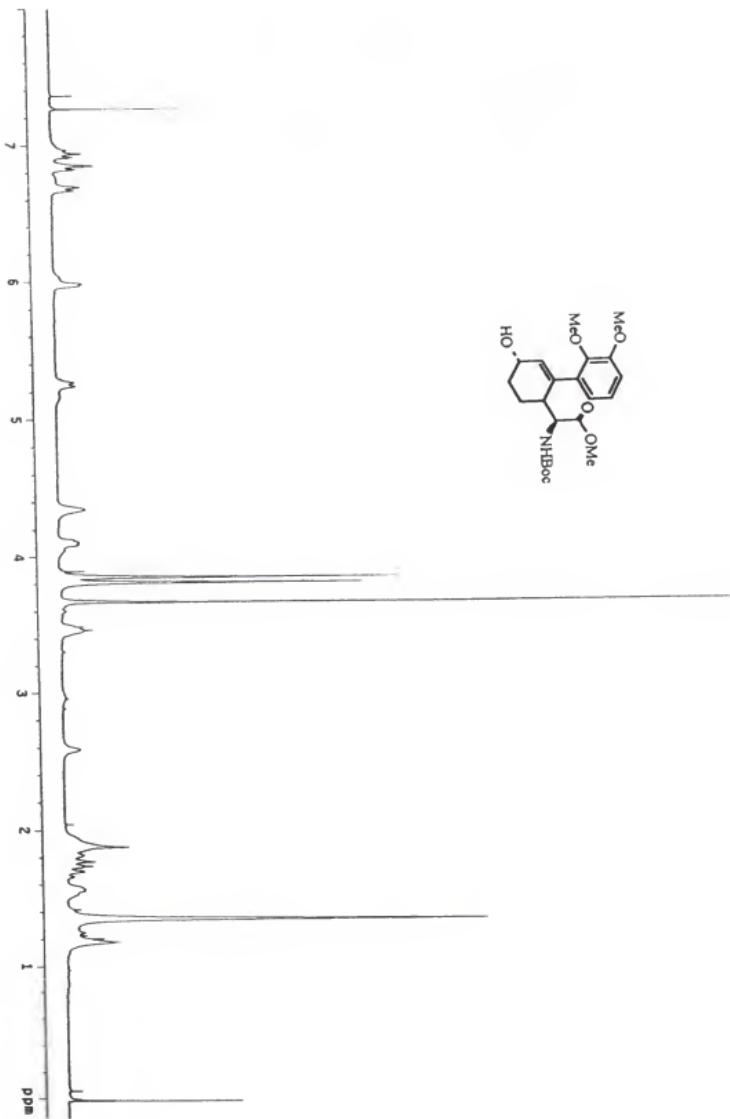
220 200 180 160 140 120 100 80 60 40 20 0 pps



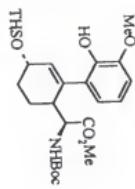
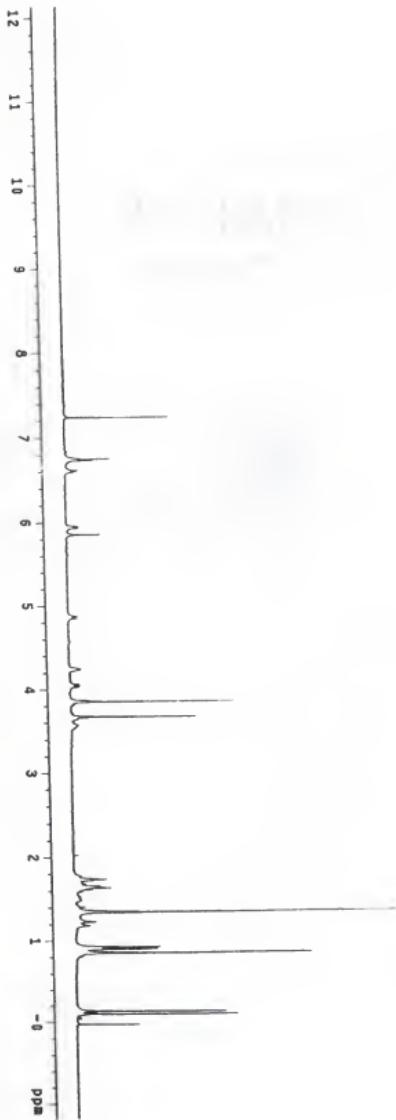
amines  
 Pulse Sequence: \*2pu1  
 Solvent: CDCl<sub>3</sub> / 298.1 K  
 WIDENING: 300 "msecv300"  
 PULSE: 90.1 degrees  
 PULSE: 1.00 sec  
 ACQ. TIME: 4.168 sec  
 VETRIM: 3333.1 Hz  
 OBSERVE: H1: 208.7753600 MHz  
 DATA PROCESSING: 1.423 sec  
 FID: 1 sec  
 Total time: 7 sec

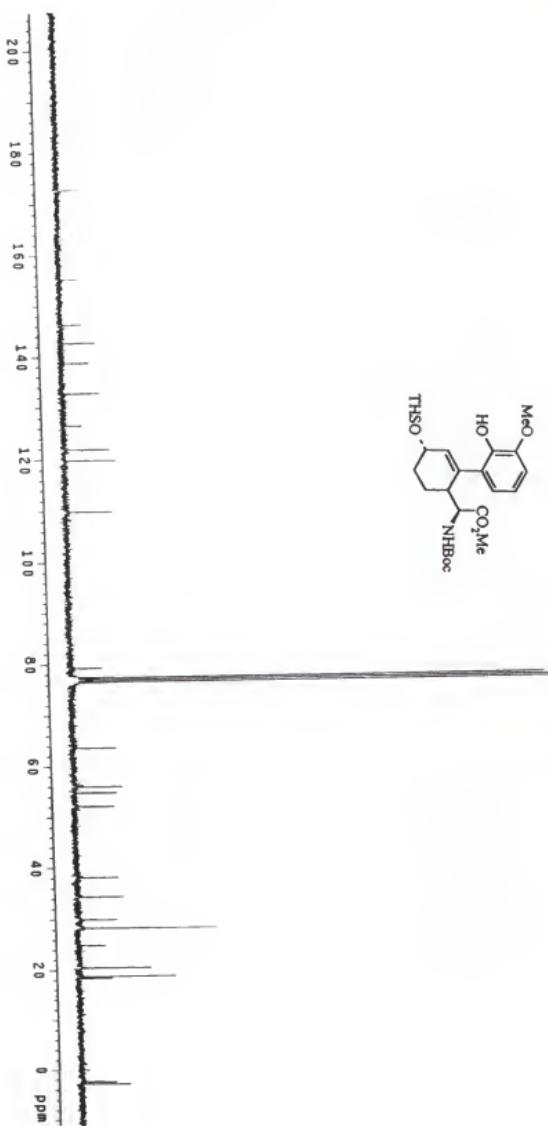












37

Pulse sequence: opt

SOVANT CUTS  
Temp. 25.0 C / 298.1 K

MERCURY-300, MURRAY

Polar alignment up  
1st pulse 180.0 degrees  
2nd pulse 35.5 degrees

and pulse width 1.816 sec  
acq. time 1.816 sec  
width 1955.05 Hz  
2126 transients

OBSERVE C12: 75-3660036

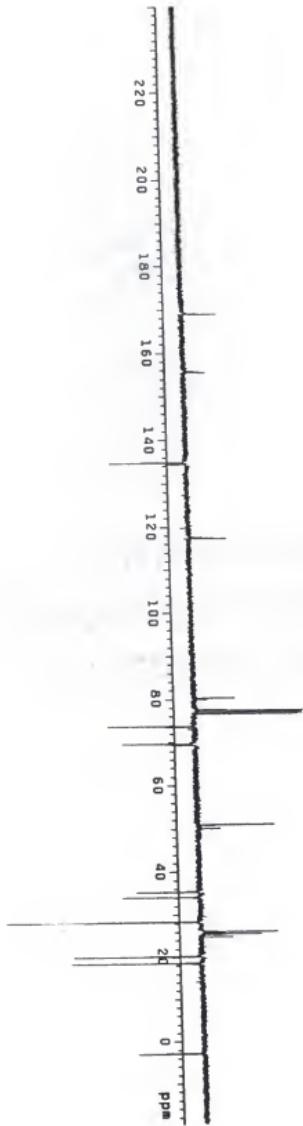
DICUPLA MI, 2000/1999 2000  
Power 43 dB

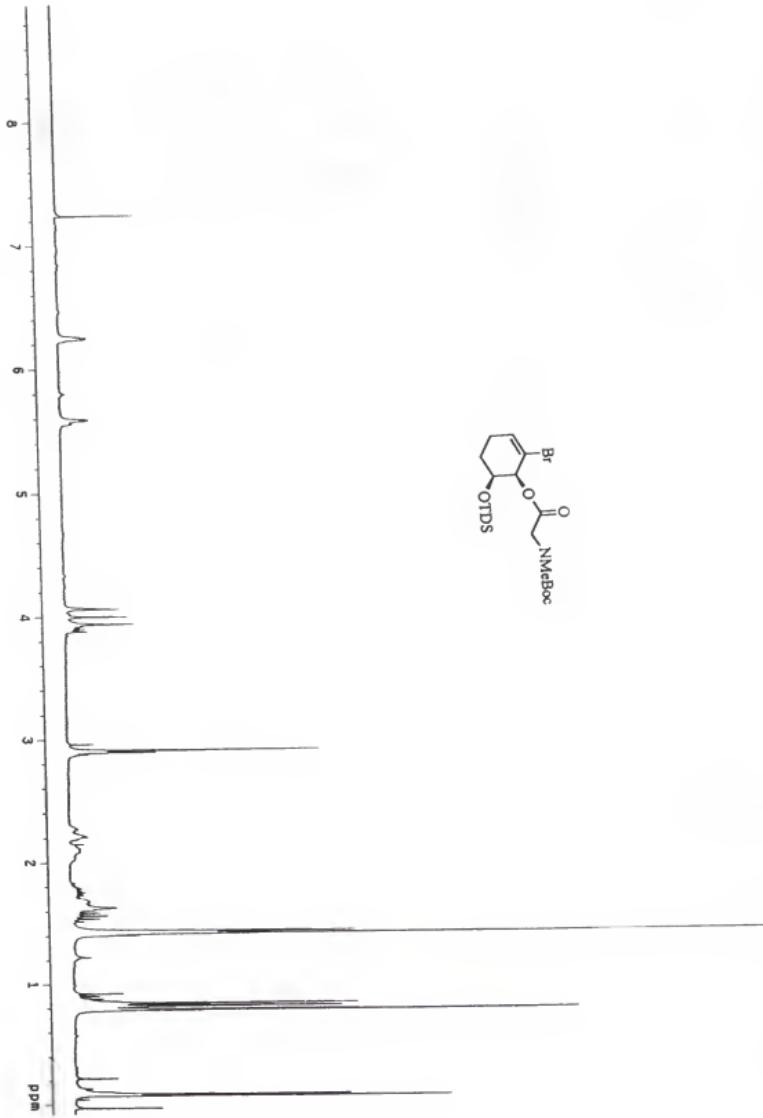
on during acquisition  
WALTZ-16 modulated

DATA PROCESSING  
Line broadening 1.0 Hz

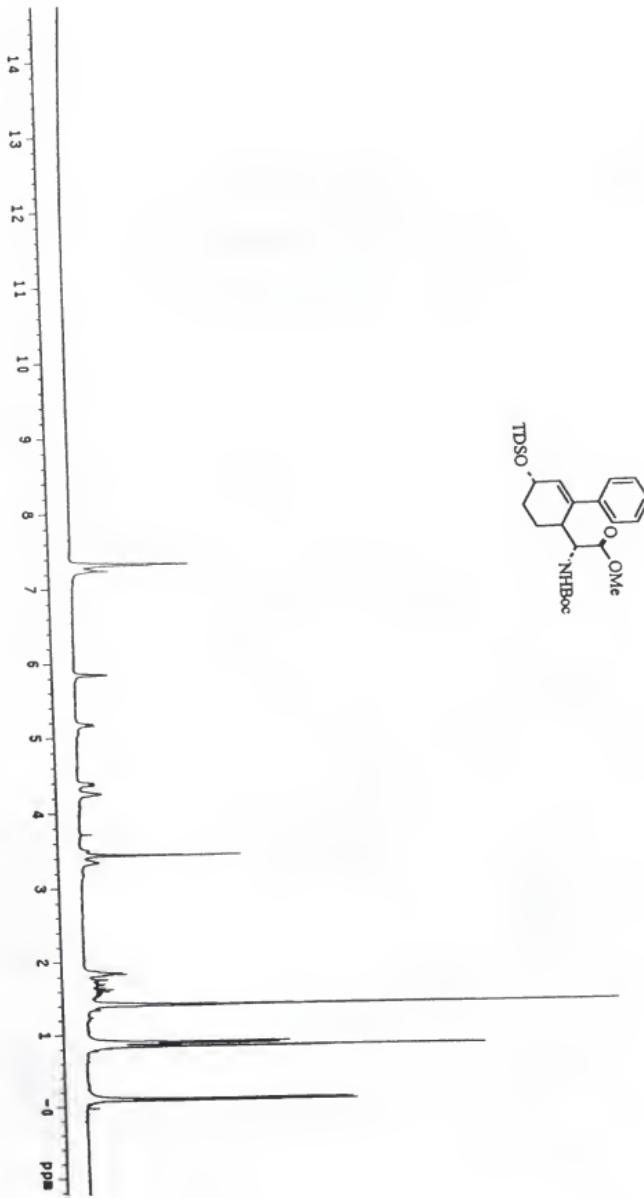
FY 83-84: 11/10/72 Total time 1 hr. 53 min. 1 sec.

The chemical structure shows a cyclohexene ring substituted with a 2-bromo-2-methoxyethyl group at the 1-position. The substituent consists of a methylene group (CH<sub>2</sub>) attached to a bromine atom (Br) and a methoxy group (OCH<sub>3</sub>). The methoxy group is further attached to a carbonyl group (C=O), which is part of a N,N-dimethylbutyl ester side chain (OTDS).





PULS: STEVENS, PFGN  
Pulse: 22.7 deg/sec  
Accq. time: 1.0 sec  
16 repetitions  
Observe: H1 300.0673923 MHz  
Data processing: 0.2 Hz  
Line broadening: 1.780 sec  
RT size: 65536  
Total time: 0 min, 0 sec



Pulse Sequence: opt

Solvent: CDCl<sub>3</sub>

ambient temperature

RI = Varian Mercury 3001

Marconi 300 MHz NMR

PALE: 80.0, 90.0 degrees

PADE: 81.7, 90 degrees

2nd pulse 23.7 degrees

Ach. time 1.01 sec

Width 1.00 Hz

Width 1.00 Hz

Observe C13: 75.374198 Hz

Decouple H1: 208.784870 Hz

Power 4.3 dB

Integration 0.00

WID: 7.71 Hz

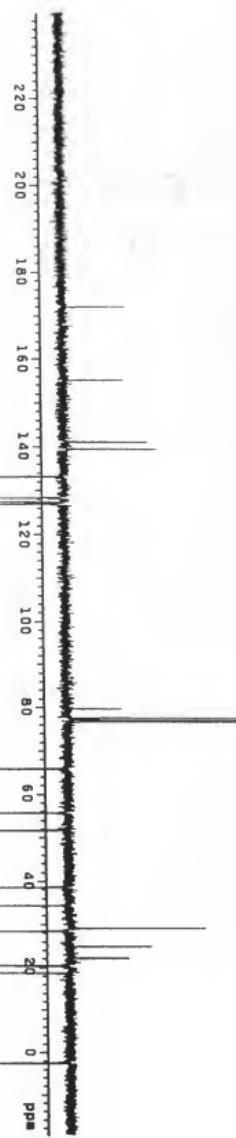
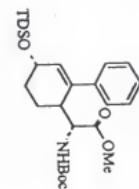
Modulated

Data Processing 1.0 Hz

Line broadening 1.0 Hz

Total time 0 min, 0 sec

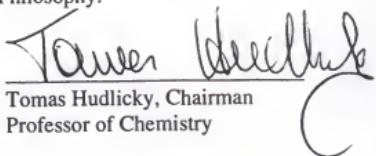
Time constant 0 sec



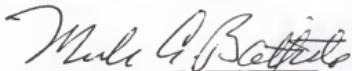
## BIOGRAPHICAL SKETCH

Kofi Oppong was born in Islington, England on July 10, 1969. He attended elementary school at St. Martin de Porres School and high school at Accra Academy and Okuapeman Secondary School in Accra Ghana. He obtained admission to the University of Indianapolis in 1989 to study Organic Chemistry under both an athletic and a Presidential scholarship. After completing requirements for an Associates Degree in Chemistry, he obtained employment at DowElanco Pharmaceuticals now Dow AgroSciences working as a chemistry technician. At DowElanco he worked in the area of fluorine chemistry under Professor Melvin Druelinger of the University of South Colorado on sabbatical at DowElanco during that time. Upon completion of his Bachelor of Science degree in chemistry he decided to pursue graduate studies in Organic Chemistry specifically in the natural product synthesis area under the direction of Professor Tomas Hudlicky at the University of Florida. His Ph.D research has focused on chemoenzymatic approaches to the synthesis of molecules of different complexity. His major area of focus has been in the synthesis of morphinan intermediates utilizing a combination of enzymatic and basic synthetic organic chemistry methods. After graduate school he plans to pursue a career in industry as a medicinal chemist. His life goal is to be directly involved in the synthesis of one major drug.

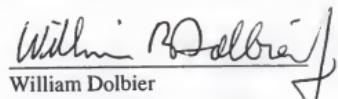
I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

  
Tomas Hudlicky, Chairman  
Professor of Chemistry

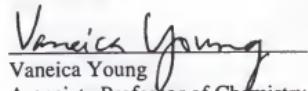
I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

  
Merle Battiste  
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

  
William Dolbier  
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

  
Vaneica Young  
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

  
Howard Johnson  
Professor of Microbiology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

  
Dennis Wright  
Professor of Chemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 2001

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Dean, Graduate School